BMJ Open

Patient and Provider's perspective on barriers and facilitators for medication adherence among adult patients with Cardiovascular Diseases and Diabetes Mellitus in India – A qualitative evidence synthesis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055226
Article Type:	Original research
Date Submitted by the Author:	06-Jul-2021
Complete List of Authors:	Krishnamoorthy, Yuvaraj; JIPMER PSM, Rajaa, Sathish; Jawaharlal Institute of Postgraduate Medical Education, Rehman, Tanveer; Public Heath Specialist Thulasingam, Mahalakshmi ; JIPMER, Department of Preventive and Social Medicine
Keywords:	QUALITATIVE RESEARCH, PREVENTIVE MEDICINE, PRIMARY CARE, Coronary heart disease < CARDIOLOGY, DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Patient and Provider's perspective on barriers and facilitators for medication adherence among adult patients with Cardiovascular Diseases and Diabetes Mellitus in India – A qualitative evidence synthesis

Running head: Barriers and facilitators for medication adherence among CVD and DM patients in India

Article category: Systematic Review

Yuvaraj Krishnamoorthy[1], Sathish Rajaa[2], Tanveer Rehman[3], Mahalakshmy Thulasingam[4]

[1]Assistant Professor, Department of Community Medicine, ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India;

Contact Number: +91 9551892665

Email id: yuvi.1130@gmail.com

[2]Assistant Professor, Department of Community Medicine, ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India;

Contact Number: +91 9791974633

Email id: psrajaa2410@gmail.com

[3]Independent Author, Kolkata, West Bengal, India

Contact Number: +91 8336922482

Email id: drtanveerrehman@gmail.com

[4]Associate Professor, Department of Preventive and Social Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry - 605006, India;

Contact Number: +91 9488729774

Email id: mahalakshmi.dr@gmail.com

Corresponding Author:

Dr Sathish Rajaa,

Assistant Professor,

Department of Community Medicine,

ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India

Contact Number: +91 9791974633

Email id: psrajaa2410@gmail.com

Strengths and Limitations:

- This is the first review exploring factors associated with drug adherence among CVD & DM patients in India
- Patient-related barrier was lack of knowledge about their condition, forgetfulness, stigma and stress
- Care team-related barrier was lack of family support, risk communication and physician attitude
- Health system-related barriers were accessibility, affordability, availability and acceptability
- Solutions to address these barriers were peer support group, digital reminders and innovations in patient care

Abstract:

Background:

In spite of recent technological and pharmacological advancements to treat and monitor diabetes mellitus (DM) and cardiovascular disease (CVD) patients, medication adherence is of particular concern in countries like India. Hence, this review was done to explore the various stakeholders' perspective on barriers and facilitators for medication adherence among CVD and DM patients.

Methods:

A comprehensive systematic search was conducted in Medline, Cochrane library, ScienceDirect and Google Scholar from January 2010 to July 2020. We used framework for systems approach to healthcare delivery to conduct thematic analysis and derive relevant themes, sub-themes and codes.

Results:

In total, 18 studies were included. Major barrier reported was lack of understanding about the disease, complications related to non-adherence, and treatment schedule followed by forgetfulness, lack of family support and risk communication. Health system-related barriers such as accessibility, affordability, and acceptability were also reported by majority of the studies. Creation of peer support group, digital reminder system, integration of AYUSH, mental health, physiotherapy and geriatric clinics at primary healthcare level and innovations in patient care were suggested to counter these barriers in medication adherence.

Conclusion:

Such targeted interventions should be developed to achieve better control among CVD and DM patients.

Keywords: Cardiovascular Diseases, Diabetes Mellitus, Medication Adherence, Qualitative Research

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality globally and in India.[1,2] More than a quarter (28%) of all deaths in India are attributable to CVDs with Ischemic heart disease (IHD) and stroke constituting the majority (83%).[3] On the other hand, India ranks second after China in the global diabetes epidemic, with a prevalence of around 10%.[4] Both diabetes mellitus (DM) and hypertension have long been recognized as independent risk factors for CVDs, whereas adherence to prescribed hypoglycaemic and antihypertensive drug therapies have significantly reduced the risk.[5–7] At least half of hypertensive & DM patients stop taking their medication within a year, often without informing their provider, with further attrition over time accomplishing medication adherence a significant public health priority.[8] Medication adherence is defined as the extent to which a person's behaviour coincides with the agreed medication regimen or health advice from a health care provider.[9] It has three components: initiation (when the patient takes the first dose of prescribed medication), implementation (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen), and discontinuation (when no more doses are taken after that).[10] Medication adherence is of growing interest to clinicians, healthcare systems, and other stakeholders (e.g., payers). There is soaring evidence that nonadherence is often associated with lower quality of life, adverse clinical events, increased need for medical interventions, mortality, and eventually avoidable healthcare out-of-pocket expenditure.[11] Non-adherent hypertensive and stable coronary heart disease (CHD) patients have a five and four times higher risk of developing CHD and death when compared to adherent patients.[12,13] Similarly, the likelihood of hospitalization is doubled among DM & hypertensive patients who are non-adherent to prescribed therapies compared with the general population. Despite recent advancements in pharmacologic treatment and technology to treat and monitor DM and CVD patients,

medication adherence is of particular concern in low-and-middle-income countries (LMIC) like India, where accessibility and affordability are still issues.[3,14]

Barriers to adherence can be comprehended as the patient, medication, provider, and health system factors with interactions among them.[15,16] Patient factors that influence adherence include poor health literacy, cultural beliefs regarding medication effectiveness, and religious healing practices.[16] Low income, forgetting to take medication, and perceptions regarding pills like safety concerns, convenience, and necessity add to the above list.[15,16] Inadequate knowledge about a drug and its use, not being convinced of the need for medication, fear of adverse effects, and long-term treatment regimens also prompt medication discontinuation.[14] Clinician factors cover failure to recognize nonadherence, prescription of complex and multidrug regimens, ineffective communication of benefits, and excluding patients in the treatment decision–making process.[16] Health system factors comprise limited insurance coverage, poor coordination of care between inpatient and outpatient settings, and inadequate communication between prescribers (i.e., specialists and primary care clinicians). In addition, the caregivers' aspect also becomes relevant in determining patients' adherence as CVD patients with a caregiver are more likely to be adherent to medications.[17] Hence identifying specific barriers for each patient and adopting suitable techniques to overcome them is imperative to improve medication adherence. Some of the facilitators successful in overcoming these barriers include a personal medication counsellor in the care continuum to guide patients with medication use, single-pill fixed-dose combinations, training pharmacists as coaches for drug therapies, building peer groups for chronic conditions, and developing information systems in the follow-up of patients.[18]

Quantitative studies have focused on medication adherence incidence and identification of its potential risk factors. They do not, however, uncover life circumstances that may influence adherence from the patient perspective. The inclusion of qualitative studies in our review will

provide a better understanding of the barriers and facilitators from the perspective and experiences of patients, healthcare providers, and caregivers. Furthermore, this synthesis of qualitative evidence aims to generate relevant and meaningful findings appropriate to the individuals, develop a research plan, and eventually help make an effective policy and practices in improving adherence among the patients. Therefore, the current review was done to understand the perspective of various stakeholders (patients, caregivers, and healthcare providers) on the barriers and facilitators for medication adherence among CVD and DM patients in India. We also explored the suggestions and solutions provided by these stakeholders in overcoming the reported barriers.

METHODS

This review was performed by adhering to the "enhancing transparency in reporting the synthesis of qualitative research (ENTREQ)" statement.[19] We registered our protocol in the PROSPERO database (Registration number - CRD42020199529). We also searched PROSPERO and Cochrane to ensure that no similar review protocol has been reported. We also performed a preliminary search to ensure that no previous reviews of our similar topic targeting the Indian population were published.

Study design

We performed an evidence synthesis of the available qualitative evidence on the barriers and facilitating factors for medication adherence among CVD and DM patients. This review helped synthesize the evidence of peer-reviewed articles in this field and built an organized empirical research outline based on prior knowledge.

Eligibility criteria

Study type

We have included qualitative peer-reviewed studies conducted in India for our current review. Furthermore, qualitative evidence from other mixed methods studies was screened for eligibility and included in the qualitative component was relevant to our review. In addition, we included studies using qualitative techniques for data collection such as focussed group discussion (FGD), in-depth interviews (IDI), and Key Informant Interviews (KII).

Participant type

We have included the studies reporting the barriers and facilitators of medication adherence from patients' perspectives (CVD and DM), family members, healthcare workers (HCWs), or health system policymakers in India. HCWs were defined as per WHO recommendation as "all the persons involved in the actions whose primary intent is to enhance the health."[20]

Outcome

The phenomenon of interest in our review was the barriers and facilitators for medication adherence among CVD and DM patients and the suggestions and solutions to address the barriers and improve compliance as experienced by the patients, caregivers, family members, HCWs, and other relevant stakeholders.

Exclusion criteria

We have excluded the studies not available in English, books or conference abstracts or grey literature, or editorial comments. We have also excluded the studies reporting only quantitative data such as cross-sectional surveys, case-control, cohort studies, or intervention trials.

Search strategy

We have conducted a comprehensive and systematic search in databases and search engines such as Medline, Cochrane library, ScienceDirect, and Google Scholar. A combination of medical subject heading (MeSH) and free-full text terms was used for carrying out a literature search. The detailed search strategy and search results in the databases mentioned above and search engines are provided in Supplementary File 1. In addition to this, we also checked the

reference list of primary studies obtained via electronic search and included articles relevant to our review and analysis. The search was conducted in all the databases from January 2010 to July 2020 with English language restriction for publication. Furthermore, the search timeline was restricted to ensure that our work provides a broader view and identifies the emerging issues.

Study selection process

Two investigators (YK and TR) independently performed the literature search, screened the title and abstract of all the identified studies, and retrieved the full text for articles relevant to our review. Further full-text screening of the retrieved articles was done again independently by the two investigators (YK, TR) to select the studies matching the eligibility criteria of our review. Disagreements during this process between the two investigators were resolved through consultation with a third investigator (SR).

Data Extraction and Management

After the study selection, two investigators (YK and TR) independently extracted the relevant data and study characteristics onto a predetermined data extraction format. Data entry was double-checked for accuracy by a third investigator (SR) by comparing the data presented in the review and individual study reports. As a result, we have extracted the following study characteristics: general information such as the name of the first author, the country in which the study was done, and year of publication, in the methods section, data collection period, study design, study participants, sample size, sampling technique, and data collection procedure. In addition, barriers, facilitators, suggestions, and solutions to medication adherence were identified systematically.

Quality assessment

Two investigators (YK and SR) independently performed the quality check using the Critical Appraisal Skills Programme (CASP) criteria.[22] This checklist has been widely used for

assessing the quality of studies included in this Qualitative Evidence synthesis. This has helped determine whether the studies included are coherent with the quality appraisal standard for qualitative studies. This checklist consists of 10 questions concerning the study's clarity, methodology, and results to rank the included studies. Subsequently, these studies were stratified into high quality (three stars for studies scoring 8 to 10 points), medium quality (two stars for studies scoring 4 to 7 points), and low rate (one star for studies scoring 0 to 3 points). We did not exclude the low-quality studies, but the interpretation of results was made with caution. Disagreements during the quality assessment process were resolved by discussion with the third investigator (TR).

Data Analysis

We analysed and reported the findings in separate clusters such as patients, caregivers, family members, HCWs, and policymakers to demonstrate the differences among these subgroups. We have adopted a thematic framework analysis to analyse and synthesize the data. Thematic framework analysis has been helpful as the evidence was primarily descriptive and improved our understanding of the barriers and facilitators in medication adherence among CVD and DM patients, and helped to identify the solutions for the same. This framework synthesis has five stages of synthesizing the qualitative data.

First stage - Familiarisation with the data: Primary investigator (YK) did the process of familiarisation with data by reviewing all the selected articles against the objective of our review and found the recurrent themes across the included studies.

The second stage - Identifying the thematic framework: The investigators used a predetermined thematic framework developed using literature to guide the thematic analysis. However, we have adopted this thematic framework based on the themes emerging in our research. This final framework has provided a detailed list of facilitators and barriers for medication adherence and also solutions to address the issue.

Third stage - Indexing: Two independent investigators (YK and TR) have read the extracted information and searched for the themes as per the predetermined thematic framework and additional emerging themes. The framework underwent several revisions as and when a new theme emerged. This has been performed through discussion and agreement between the entire team of investigators. Next, all the studies were completely read and examined till there was no new emergent theme. Coding of the data was then done as per the themes identified in our analysis. Finally, each preliminary study indexing was done using the codes related to the thematic framework. Whenever appropriate, sections of the studies were indexed with one or more codes.

Fourth stage - Charting: The investigators have sorted the data based on the themes and presented these themes in the tabular format (chart). The rows and columns of the table indicate the themes related and the studies, which enabled us to compare the study findings across various themes and subthemes.

***Fifth stage - Mapping and interpretation*:** The investigators used these charts to define the concepts identified and mapped the nature and range of phenomena. Our review explored the associations between the various themes and helped in clarifying the findings. Finally, we mapped and interpreted the findings in line with our objectives and emergent themes.

Patient and Public Involvement:

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Results

Study selection

A comprehensive and systematic search was done to identify the relevant studies from January 2010 to July 2020. In total, we identified 1187 citations, and after the removal of duplicates

from multiple databases, 982 records were screened for their title and abstract and assessed for eligibility. From these records, we retrieved 33 articles, and after going through the full text of these articles, 18 studies were included in the review. (**Figure 1**).[22-39]

Characteristics of the studies included

Characteristics of the included studies are reported in **Table 1**. Of the 18 studies included, 9 (50%) were from the Southern region, followed by 7 (38%) from the Northern part of India. The mean age of the participants ranged from 25-76 years. The typology of the studies comprised of in-depth interviews (IDIs) and focussed group discussions (FGDs). The study participants were primarily patients with diabetes, hypertension, or any cardiovascular diseases (to explore the patient perspective), and health care workers (4 studies) providing care to them (to obtain the provider perspective). The total sample size of the included studies ranged from 6 to 100. The majority (10 of the included studies) were done in a community setting, while the rest were either facility-based or had participants from ongoing trials. Four of the included studies used software for analysing the qualitative data, while the rest followed manual methods. Most of the included studies (14 out of 18) had higher ratings indicating high-quality evidence.

Narrative synthesis

Significant findings from the review showed that factors contributory to adherence come under three themes: patient-related, family-related, and health system-related factors. The barriers, facilitators, and suggestions to improve medication adherence were summarized under these three themes.

Barriers in medication adherence

Table-2 shows the thematic framework analysis related to barriers in medication adherence among CVD and DM patients. All the 18 included studies have explored and reported on these barriers.

Patient-related factors

A significant patient-related barrier (10 studies) reported was a lack of knowledge or understanding about the disease, its complications related to nonadherence, and the treatment schedule. The following common patient-related barrier (7 studies) was the forgetfulness to take medicine. Reasons provided for the same were the patients' busy schedule, laziness, or forgetting to take the medication while traveling out-of-station. Patients have also reported certain misconceptions about the medicines like the risk of long-term neurological illness because of medication intake, inferior quality of drugs provided in hospitals, and wrong perception about stopping the medications once the patient feels normal. Patients in some studies have reported that they practice alternate systems of medicine such as herbal medicines and avoid taking allopathic medicines leading to poorer control of their condition. Substance use such as alcohol or tobacco use, side effects related to drugs, stress, and stigma were reported to be some of the barriers by the patients in adhering to the medications.

Family-related factors

The patients and providers have reported a lack of family support as a significant contributing factor for nonadherence. For example, there was a lack of support provided by family members or caregivers in reminding the patient to take medications or accompanying the patient for a visit to healthcare facilities. In addition, the lack of social and emotional support to the patients further contributes to the nonadherence among the patients suffering from CVDs and DM. Domestic works, personal priorities, commitments, or other issues hinder the family members from providing the above-mentioned support to the patients.

Health system-related factors

In most of these studies, providers were also interviewed to understand the factors related to the health system responsible for nonadherence among CVD and DM patients. Healthcare providers and patients interviewed in almost all these studies have reported affordability,

accessibility, and acceptability as the major factors hindering medication adherence. Affordability is an issue with patients seeking healthcare in private facilities and patients getting care in public healthcare facilities. Though there is no direct medical cost related to government hospitals or primary healthcare centres, direct non-medical costs such as transport (due to poor accessibility) and indirect costs such as loss of wages (due to inconvenient consultation timing) were higher amongst these patients. In addition, patients have a wrong perception that medications in public facilities are of poorer quality, making them choose private health facilities, including those belonging to lower socioeconomic status. Lack of risk communication, counselling, or empathy by the physicians mainly due to overburdening public health facilities and time constraints were the other health system-related barriers reported by the providers and patients.

Facilitators in medication adherence

Facilitators in medication adherence were also summarized using the pre-existing thematic framework (**Table-3**). In total, ten studies have explored the facilitators in medication adherence from the patient or providers' perspective.

Patient-related factors

Most of the studies (5 studies) reported fear of complications due to nonadherence and self-perception of being healthy (once they adhere to the medications) as the significant facilitators. In addition, having a reminder system in the form of reminder notebook, separate pillboxes/cases/covers or personalized shelf facilitate the patients in adhering to the medications. Some studies have also reported that integrating drug intake into daily routine activities and peer influence acts as a good facilitator in compliance with medications.

Family-related factors

Family support was reported as a major facilitating factor for compliance with medication. Apart from the support, adverse experiences in the past, such as death or severe complications

among the family members, instilled fear in the patients, making them more compliant to the medications.

Health system-related factors

Barriers reported in some of the studies, such as empathy and counselling by healthcare providers, were considered facilitators by the other studies' patients. Another major facilitator from the health system side is the trust that patient has on their physician and follow the advice related to self-care and adherence effectively. Other familiar facilitators reported by the patients and providers were the dedicated pill cover/boxes for each drug provided in the clinic, linkage of health services with NGO for provision of counselling and generating awareness, availability of medication, and use of polypills.

Suggestions to improve medication adherence

Suggestions and solutions to enhance the compliance to medication were reported in 16 out of the 18 included studies based on either patient or provider's perspective (**Table-4**). Few suggestions were related to patients and family members, while the majority were related to the change in the health system.

Patient and family-related factors

Creating or joining a peer support group was one of the major suggestions related to the patients. This will help by motivating the patients to be more compliant with medications and other self-care practices. Digital reminder systems using a watch and a mobile phone can also improve medication adherence. Related to family members, social, emotional, and financial support to the patients has been reported as an essential suggestion by most studies.

Health system-related factors

Innovations in patient care have been necessitated as an important factor to promote drug adherence. This is mainly because the barriers reported by the patients were almost similar across the studies, and the interventions followed till now don't seem to address these issues.

Some of the innovations suggested were dedicated days for specific disease conditions to avoid overburdening the facilities, a dedicated counselling station for drug adherence during the clinic with separate human resources as the physician has time constraints during the clinic, and a unique pill dispensing mechanism like colour coding, etc. In addition, information Education and Communication (IEC)/Behaviour change communication (BCC) campaigns, digitalizing the patient treatment record, linkage of healthcare services with NGOs or community-based organizations, regular training of healthcare workers, and promotion of polypill use were other common suggestions offered by the healthcare providers.

Discussion

We conducted this review to integrate the qualitative evidences on barriers and facilitators for medication adherence among CVD and DM patients in India. We also further explored the suggestions to improve the same. The studies included in our review involved a total of 636 participants (534 CVD and DM patients, 102 healthcare providers). Majority of the included studies were of high quality with respect to study clarity, methodology and results. We summarized under three major themes: barriers, facilitators, suggestions and reported the findings under the following four sub-themes: patients, care team, healthcare organization and environment-related factors.

Comparison of findings with previous literature

Barriers in medication adherence

Major barriers were lack of patient's understanding about the disease and its complications, forgetfulness and misconception about the medications. lack of family support was seen as a major barrier from both patient's and provider's perspective. In addition to these factors, stress and stigma were also mentioned as an important factor for the patients to not take medicine on time. We also found major health system related barriers such as lack of accessibility, availability, higher cost and poor physician attitude. These findings were in line with the

previous review conducted among South East Asian DM patients.[40] In addition, our findings were also similar to the patients belonging to non-English speaking Hispanic, South American ethnic group, as they also had misconceptions related to therapy, lack of understanding about their condition, stress and stigma as a factor for non-adherence.[41-43]

Facilitators in medication adherence

Fear of complications, self-perception of being healthy, having a reminder system were reported as the major facilitators by patients. Physician trust, advice, empathy, counselling was some of the provider-related facilitators in adhering to medications. Common facilitators reported by the patients and providers were the dedicated pill cover/boxes for each drug provided in the clinic, availability of medication and use of polypills. These findings were also in line with the previous qualitative reviews conducted in low middle-income countries including India.[41-43]

Suggestions to improve medication adherence

The solutions provided by the patients and health professionals were in line with the barriers identified in our review. Proper physician counselling to make the patients understand about their own condition, complications and avoid misconception about the drugs and its side effects, good family support, making the medication accessible and available free of cost were suggested as major suggestions to improve medication adherence. Similar interventions were also suggested by previous qualitative evidences on medication adherence among CVD and DM patients.[40-43]

Strengths and limitations of the study

To the best of our knowledge, this is the first review exploring and synthesizing the qualitative factors associated with medication adherence among CVD and DM patients in India. We provided a comprehensive and systematic evidence on the barriers, facilitators related to medication adherence, adhering to the ENTREQ statement and ensuring transparency and

reproducibility of our findings. We examined these evidences through the lenses of well-established theoretical framework model. Moreover, our study was able to provide valuable suggestions to promote the medication adherence from both patients and provider's perspective. In addition to these strengths, we found that the highest rated studies contributed to majority of the factors found in our review. This in turn ensures the transferability (external validity) of our review findings.

However, our review has certain limitations. We did not search the grey literature, possibly missing some insights for our review. Hence, we cannot rule out of the dissemination bias with respect to accurate and complete representation of phenomenon of interest. We focussed primarily on the patient and provider perspective on medication adherence.[44] Hence, we cannot comment on the organizational or political influences on the adherence to long-term therapies as mentioned in the WHO report.[16] The sample size of the included studies can be considered as relatively low (median sample size - 30). However, all the studies were conducted till the achievement of data saturation.

Implications for clinical and public health practice

Improving medication adherence is essential to achieve better control and prevent life-threatening complications. Factors related to patients such as self-awareness and fear about the condition and its complications acted as major facilitator for medication adherence. We also found certain modifiable barriers related to medical intake such as forgetfulness, lack of knowledge, and misconception about medications. Interventions should focus on these modifiable barriers such as knowledge barriers, intention barriers and health system-related barriers to achieve better adherence. In addition, it is important for the family members to help the patients in mapping the daily routine and link the medicine intake with these routines to facilitate the adherence. Our review also suggested that healthcare providers play an important role in promoting the medication adherence. Hence, the interventions should not only target

the patients, but also the family members and healthcare providers and it should be tailored to the differences in setting, culture and type of the patients.

Implications for future research

More evidences need to be generated with respect to the solutions obtained in our review such as memory tools including the digital solutions, polypills, peer support groups etc. Further qualitative studies including the subgroup of patients with CVD and DM under different stages and treatment regimens and are required to contextualize the medication adherence. Exploring the barriers using theoretical framework with the same methodological approach, can provide a more reliable evidence to develop patient-centered interventions and achieve better control among CVD and DM patients.

Ethics and consent: Not applicable

Funding: None

Competing interests' statement: None declared

Acknowledgements: None

Author contribution statement: Conceived and designed the study: YK & SR, Data management and extraction: YK, SR and TR, Analysed the data and wrote the paper: YK, SR, TR and MT, Provided comments and inputs to revise the manuscript: YK, SR, TR and MT

Data sharing statement: Data will be available upon reasonable request by investigators

Word count: 4070 (Being a Qualitative Evidence Synthesis we had to quote regarding the studies in our results and also we had elaborated the methods in an elaborate manner)

References:

1. Walker IF, Garbe F, Wright J, Newell I, Athiraman N, Khan N, et al. The Economic Costs of Cardiovascular Disease, Diabetes Mellitus, and Associated Complications in South Asia: A Systematic Review. Value Health Reg Issues. 2018;15:12–26.
2. Glovaci D, Fan W, Wong ND. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. Curr Cardiol Rep. 2019;21:21.
3. Prabhakaran D, Jeemon P, Sharma M, Roth GA, Johnson C, Harikrishnan S, et al. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018;6:e1339–51.
4. Tandon N, Anjana RM, Mohan V, Kaur T, Afshin A, Ong K, et al. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018;6:e1352–62.
5. Durand H, Hayes P, Morrissey EC, Newell J, Casey M, Murphy AW, et al. Medication adherence among patients with apparent treatment-resistant hypertension: systematic review and meta-analysis. J Hypertens. 2017;35:2346–57.
6. Polypharmacy and Medication Adherence in Patients With Type 2 Diabetes | Diabetes Care [Internet]. [cited 2020 Jul 30]. Available from: https://care.diabetesjournals.org/content/26/5/1408.short
7. Vrijens B, Antoniou S, Burnier M, de la Sierra A, Volpe M. Current Situation of Medication Adherence in Hypertension. Front Pharmacol [Internet]. 2017 [cited 2020 Jul 31];8. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2017.00100/full

8. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence. 2016;10:1299–307.
9. Leporini C, De Sarro G, Russo E. Adherence to therapy and adverse drug reactions: is there a link? Expert Opin Drug Saf. 2014;13 Suppl 1:S41-55.
10. Lam WY, Fresco P. Medication Adherence Measures: An Overview. BioMed Res Int. 2015; 2015:1–12.
11. Kvarnström K, Airaksinen M, Liira H. Barriers and facilitators to medication adherence: a qualitative study with general practitioners. BMJ Open. 2018;8:e015332.
12. Ferdinand KC, Senatore FF, Clayton-Jeter H, Cryer DR, Lewin JC, Nasser SA, et al. Improving Medication Adherence in Cardiometabolic Disease. J Am Coll Cardiol. 2017;69:437–51.
13. Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. Adv Ther. 2005;22:313–56.
14. Dennis T, Meera NK, Binny K, Sekhar MS, Kishore G, Sasidharan S. Medication adherence and associated barriers in hypertension management in India. CVD Prevention and Control. 2011 Jan 1;6(1):9-13.
15. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. Circulation. 1997;95:1085–90.
16. WHO | ADHERENCE TO LONG-TERM THERAPIES: EVIDENCE FOR ACTION [Internet]. WHO. World Health Organization; [cited 2020 Jul 30]. Available from: http://www.who.int/chp/knowledge/publications/adherence_report/en/

17. Aggarwal B, Liao M, Mosca L. Medication Adherence Is Associated with Having a Caregiver Among Cardiac Patients. Ann Behav Med Publ Soc Behav Med. 2013;46:237–42.

18. Daliri S, Bekker CL, Buurman BM, Scholte op Reimer WJM, van den Bemt BJF, Karapinar – Çarkit F. Barriers and facilitators with medication use during the transition from hospital to home: a qualitative study among patients. BMC Health Serv Res. 2019; 19:204.

19. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012; 12:181

20. Mohanty A, Kabi A, Mohanty AP. Health problems in healthcare workers: A review. Journal of family medicine and primary care. 2019 Aug;8(8):2568.

21. Critical Appraisal Skills Programme (2018). CASP (Qualitative) Checklist. [online] Available at: https://casp-uk.net/wp-content/uploads/2018/01/CASP-Qualitative-Checklist-2018.pdf Accessed: 12 September 2020

22. Agarwal A, Davies D, Goenka S, Prabhakaran D, Huffman MD, Mohanan PP. Facilitators and barriers of heart failure care in Kerala, India: A qualitative analysis of healthcare providers and administrators. Indian Heart J. 2019; 71(3):235–41.

23. Dhar L. Perceptions of global coronary heart disease risk, and adherence to antihypertensive treatment among low income urban women in Delhi, India (Doctoral dissertation, Curtin University).

24. George CE, Ramadas D, Norman G, Mukherjee D, Rao T. Barriers to cardiovascular disease risk reduction: Does physicians' perspective matter? Indian Heart J. 2016; 68(3):278–85

25. Gupta S, Dhamija JP, Mohan I, Gupta R. Qualitative Study of Barriers to Adherence to Antihypertensive Medication among Rural Women in India. Int J Hypertens. 2019; 2019:1–7.

26. Gupta S, Virk A, Mittal A, Agarwal B. Patterns and determinants of healthcare-seeking behavior among hypertensive patients in a rural population of north India: A mixed-method study. J Family Med Prim Care. 2020; 9(6):2830

27. Jayanna K, Swaroop N, Kar A, Ramanaik S, Pati MK, Pujar A, et al. Designing a comprehensive Non-Communicable Diseases (NCD) programme for hypertension and diabetes at primary health care level: evidence and experience from urban Karnataka, South India. BMC Public Health. 2019; 19:1

28. Krishnamoorthy Y, Giriyappa DK, Eliyas SK, Priyan S, Saya GK, Lakshminarayanan S. Patient and Provider's Experience and Perspective in Addressing Barriers to Medication Adherence Among Noncommunicable Disease Patients in Rural Puducherry, South India—A Qualitative Study. J Patient Exp. 2019; 6(3):216–23

29. Kusuma YS. Migrants' Perceptions on Barriers to Treatment Seeking for Hypertension: A Qualitative Study from Delhi, India. Studies on Ethno-Medicine. 2010; 4(3):173–6

30. Miller V, Nambiar L, Saxena M, Leong D, Banerjee A et al. Exploring the barriers to and facilitators of using evidence-based drugs in the secondary prevention of cardiovascular diseases: findings from a multistakeholder, qualitative analysis. Global Heart. 2018; 13(1):27-34.

31. Newtonraj A, Arun S, Bazroy J, Tovia S. Lay perspectives on causes and complications of hypertension; and barrier to access health care by known hypertensive patients: a qualitative study from a rural area of South India. Int J Community Med Public Health. 2017; 4(3):704

32. Nimesh VV, Halder A, Mitra A, Kumar S, Joshi A, Joshi R, et al. Patterns of healthcare seeking behavior among persons with diabetes in Central India: A mixed method study. J Family Med Prim Care. 2019; 8(2):677.

33. Pati S, Van den Akker M, Schellevis FF, Sahoo K, Burgers JS. Managing diabetes mellitus with comorbidities in primary healthcare facilities: a qualitative study among physicians in Odisha, India. 2020. Research square [preprint] doi: 10.21203/rs.3.rs-22272/v1

34. Anitha Rani M, Shriraam V. Are Patients With Type 2 Diabetes Not Aware or Are They Unable to Practice Self-Care? A Qualitative Study in Rural South India. J Prim Care Community Health. 2019; 10:2150132719865820.

35. Salam A, Praveen D, Patel A, Tewari A, Webster R. Barriers and facilitators to the use of cardiovascular fixed-dose combination medication (polypills) in Andhra Pradesh, India: a mixed-methods study. Global Heart. 2019; 14(3):303-10.

36. Satish P, Khetan A, Barbhaya D, Agarwal M, Mohan SK, Josephson R, Webel AR. A qualitative study of facilitators and barriers to cardiovascular risk factor control in a semiurban population in India. J Family Med Prim Care. 2019; 8(12):3773-3778.

37. Thakur JS, Vijayvergiya R, Jaswal N, Ginsburg A. Assessment and barriers to medication adherence for secondary prevention of cardiovascular disease among patients with coronary artery disease in Chandigarh, India. Int J Non-Commun Dis. 2016;1:37-41.

38. Venkatesan M, Dongre AR, Ganapathy K. A community-based study on diabetes medication nonadherence and its risk factors in rural Tamil Nadu. Indian J Community Med. 2018; 43(2):72-76

39. Wood F, Salam A, Singh K, Day S, Jan S, Prabhakaran D, et al. Process evaluation of the impact and acceptability of a polypill for prevention of cardiovascular disease. BMJ Open. 2015; 5(9):e008018

40. Sohal T, Sohal P, King-Shier KM, Khan NA. Barriers and Facilitators for Type-2 Diabetes Management in South Asians: A Systematic Review. PLoS ONE. 2015; 10(9): e0136202.

41. Nam S, Chesla C, Stotts NA, Kroon L, Janson SL. Barriers to diabetes management: patient and provider factors. Diabetes Res Clin Pract. 2011; 93(1):1–9

42. Lipton RB, Losey LM, Giachello A, Mendez J, Girotti MH. Attitudes and issues in treating Latino patients with type 2 diabetes: views of healthcare providers. Diabetes Educ. 1998; 24: 67–71

43. Al Hamid A, Ghaleb M, Aljadhey H, et al. A systematic review of qualitative research on the contributory factors leading to medicine-related problems from the perspectives of adult patients with cardiovascular diseases and diabetes mellitus. BMJ Open 2014; 4:e005992.

44. Toews I, Booth A, Berg RC et al. Further exploration of dissemination bias in qualitative research required to facilitate assessment within qualitative evidence synthesis. J Clin Epidemiol 2017; 88:133–139

Table 1: Characteristics of the studies included (N=18)

S.No	Author and year	State	Data collection method	Study participants	Study setting	Approach	Coding	Theoretical framework used	Method of analysis	Sample size	Mean Age in years	Study quality
1.	Agarwal 2019	Kerala	IDI	Clinical and administrative staff	Facility based	NR	Inductive	NR	Dedoose Software	21	NR	***
2.	Dhar et al 2016	Delhi	IDI	Hypertensive women aged 35-59 years	Community based	NR	Inductive	Yes	Manual content analysis	30	48	***
3.	George et al 2016	Karnataka	IDI	Physicians providing Non communicable disease care	Community based	NR	Inductive	NR	Manual content analysis	36	46	***
4.	Gupta et al 2019	Rajasthan	IDI	Hypertensive women	Facility based	NR	NR	NR	Manual content analysis	30	56	**
5.	Gupta et al 2020	Haryana	IDI	Hypertension patients	Facility based	NR	NR	NR	Manual content analysis	100	38-76	***
6.	Jayanna et al 2019	Karnataka	IDI & FGD	Diabetes and Hypertension patients	Facility based	NR	NR	Yes	Manual content analysis	10 IDI + 20 FGDs	NR	***
7.	Krishnamoorthy et al 2018	Puducherry	IDI & KII	Diabetes and Hypertension patients & Healthcare workers	Community based	NR	Inductive	NR	Manual content analysis	6 IDI + 4 KII	NR	***
8.	Kusuma et al 2010	Delhi	KII & FGD	Recent and Settled Migrants having hypertension inhabited in Delhi	Community based	NR	NR	NR	Manual content analysis	14 (KII) + 20 (FGD)	38 – 50 (KII) & 25 – 40 (FGD)	***
9.	Miller et al 2017	Delhi	IDI	Cardiovascular disease patients	Trial based	Descriptive	NR	NR	Manual content analysis	14	NR	***
10.	Newtonraj et al 2017	Tamil Nadu	Personal interviews	Hypertensive patients	Community based	NR	NR	NR	Manual content analysis	40	NR	**

11.	Nimesh et al 2019	Madhya Pradesh	IDI	Individuals with diabetes	Community based	NR	Inductive	Yes	Manual content analysis	60	52	***
12.	Patti et al 2020	Orissa	IDI	Primary care physicians	Facility based	NR	NR	NR	Manual content analysis	17	40	***
13.	Rani et al 2019	Tamil Nadu	FGD	Individuals with diabetes	Community based	Descriptive	NR	NR	Manual content analysis	50	50	**
14.	Salaam et al 2019	Andhra Pradesh	IDI	Patients with Cardiovascular disease	Community based	NR	NR	Yes	NVivo version 11 software	12	62	***
15.	Satish et al 2019	West Bengal	FGD	Patients with hypertension and/or diabetes	Trial based	NR	NR	Yes	Manual content analysis	70	53	***
16.	Thakur et al 2016	Chandigarh	IDI & FGD	Coronary artery disease patients	Facility based	NR	NR	NR	Manual Thematic analysis	20	NR	*
17.	Venkatesan et al 2018	Tamil Nadu	IDI	Health care workers	Community based	NR	NR	NR	Anthropac software	10	NR	***
18.	Wood et al 2015	Hyderabad and Delhi	IDI	Patients with Cardiovascular diseases	Trial based	NR	NR	Yes	Nvivo software	52	57	***

NR – Not Reported
IDI – In depth Interview
FGD – Focussed Group Discussion
KII – Key informant interview

Table 2: Thematic framework analysis for summarizing barriers in medication adherence experienced by CVD & DM patients in India

Main theme/Sub-themes	Barriers in Medication Adherence	Studies
PATIENTS	1. **Lack of awareness/knowledge:** Lack of knowledge and understanding about the disease, its complications and treatment among the patients	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Newtonraj et al 2017, Patti et al 2020, Tan et al 2017, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	2. Forgetfulness: Patients forget to take medicine because of busy schedule	**Dhar et al 2016, Gupta et al 2019, Gupta et al 2020, Rani et al 2019, Venkatesan et al 2018, Wood et al 2015, Tan et al 2017, Thakur et al 2016**
	3. Misconception about medications: Patient has wrong perception about the medications, especially about its side effects and quality	**George et al 2016, Gupta et al 2020, Patti et al 2020, Rani et al 2019, Salaam et al 2019, Tan et al 2017, Venkatesan et al 2018**
	4. Preference to alternate system of medicine: Patients prefers taking herbal and other alternate system of medicines for their condition	**George et al 2016, Tan et al 2017, Venkatesan et al 2018**
	5. Ill effects of substance abuse: Patients have difficulty in adhering to medications during the bout of tobacco or alcohol consumption	**Jayanna et al 2019, Krishnamoorthy et al 2018**
	6. Effect of side effects: Patients stop their medication once they develop side effects related to the drugs	**Venkatesan et al 2018, Wood et al 2015**
	7. Stress: Patients developing stress due to personal or work-related problems are more non-adherent to medications	**Krishnamoorthy et al 2018**
	8. Stigma: Patients feel stigmatised in revealing their disease status to other family/friends leading to lack of support from them	**Krishnamoorthy et al 2018**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Family support:** Lack of physical, emotional and social support as the family members are pre-occupied with domestic works, crisis, other priorities and commitments	**Dhar et al 2016, George et al 2016, Gupta et al 2020, Krishnamoorthy et al 2018, Kusuma et al 2010, Newtonraj et al 2017, Rani et al 2019, Wood et al 2015**
	2. Risk communication: Poor risk communication or counselling to patients and family members about non-adherence to medication by the treating physicians	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Thakur et al 2016**
	3. Physician attitude: Lack of respect, empathy, communication and attention towards patients bythe treating physicians	**Dhar et al 2016, Gupta et al 2019, Kusuma et al 2010, Jayanna et al 2019**

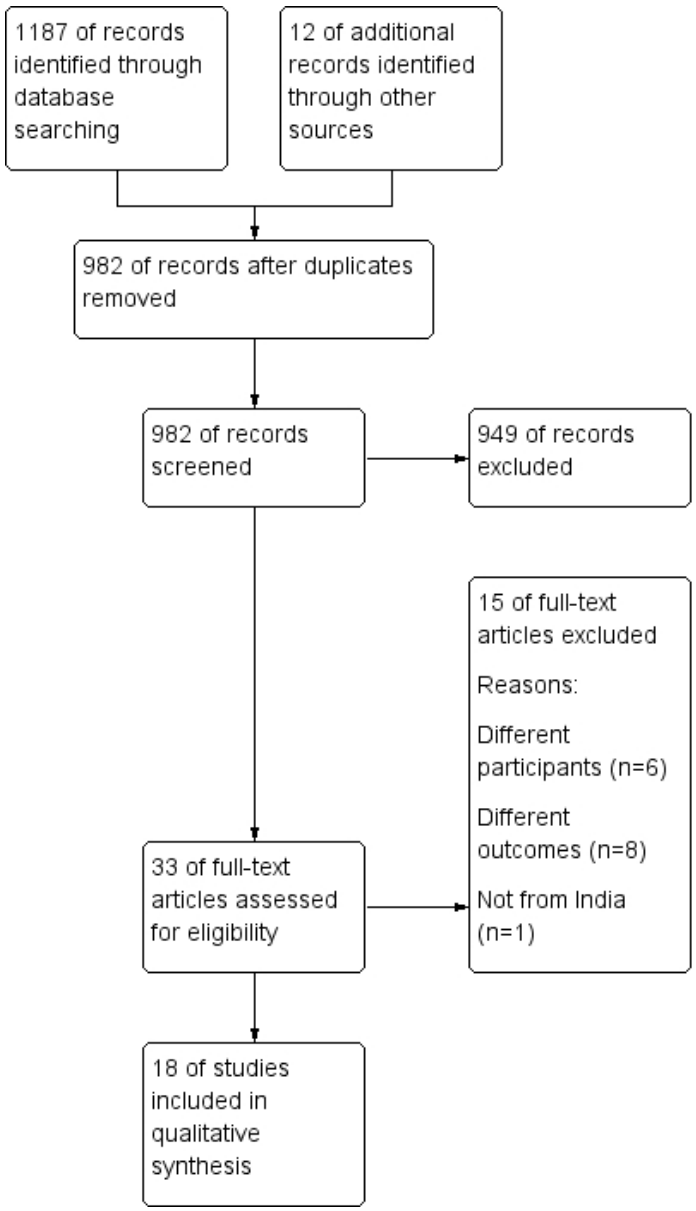
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Affordability:** Patients lose their daily wages due to inconvenient consultation timings in public facilities, which is aggravated by travel costs due to poor access, and higher medication costs while preferring private facilities	**Agarwal et al 2019, Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Kusuma et al 2010, Miller et al 2017, Nimesh et al 2019, Salaam et al 2019, Satish et al 2019, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	2. Accessibility: Lack of access to healthcare facilities (more distance) requiring longer travel and waiting time.	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Miller et al 2017, Newtonraj et al 2017, Tan et al 2017, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	3. Availability: Non-availability of essential medicines in public healthcare facilities	**Dhar et al 2016, Jayanna et al 2019, Kusuma et al 2010, Miller et al 2017, Newtonraj et al 2017, Patti et al 2020, Salaam et al 2019, Wood et al 2015**
	4. Acceptability: Medications from public health facilities are not acceptable to the patients due to poorer quality	
	5. Overburdening of primary health centres: Burdening of primary health facilities lead to time constraints in patient counselling regarding medication adherence	**Jayanna et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Patti et al 2020, Venkatesan et al 2018**

Table 3: Thematic framework for summarizing facilitators in medication adherence experienced by CVD & DM patients in India

Main theme/Sub-themes	Facilitators in Medication Adherence	Studies
PATIENTS	**1. Self-awareness and fear:** Patient's understanding about medicine adherence and fear about complications of non-adherence keeps them healthy	**Krishnamoorthy et al 2018, Miller et al 2017, Patti et al 2020, Satish et al 2019, Tan et al 2017, Wood et al 2015**
	2. Medicine Reminder system: Separate pill boxes/cases/covers, personalized shelf, and maintaining drug record notebook helps them in remembering daily doses	**Dhar et al 2016, Krishnamoorthy et al 2018, Miller et al 2017, Tan et al 2017**
	3. Integrating drug intake with the daily routine: Fixed time for medicine intake, separate place for keeping drug, and making arrangements during travel helps them in adherence	**Dhar et al 2016, Krishnamoorthy et al 2018**
	4. Positive peer influence: Good adherence to medication by the patient's peers motivates the patient to be compliance to their own drug intake	**Gupta et al 2019, Krishnamoorthy et al 2018**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Family support**: Constant reminders by family members for drug intake	**Dhar et al 2016, Gupta et al 2020, Krishnamoorthy et al 2018, Miller et al 2017, Wood et al 2015**
	2. Past adverse experiences: Death of patients' own family members due to complications of the condition has motivated them to adhere to medication	**Dhar et al 2016, Krishnamoorthy et al 2018**
	3. Healthcare provider counselling and empathy: Patients described that counselling from their healthcare providers has motivated them to remain adherent	**Kusuma et al 2010, Miller et al 2017, Patti et al 2020, Salaam et al 2019, Tan et al 2017**
	4. Trust in physician: Adherence is more when a positive rapport and trust is established between the patient and health care providers.	**Dhar et al 2016, Krishnamoorthy et al 2018, Satish et al 2019**
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Dedicated pill boxes/covers:** Provision of different medications in separate boxes/covers in the healthcare facility has helped as the patient to remember which medication to take at what time	**Krishnamoorthy et al 2018, Wood et al 2015**
	2. Combination drugs (polypills): Polypills had the following advantages to facilitate the medication adherence: a smaller number of pills, lower frequency, less chance of forgetting, potential for lower cost, and convenient simpler regimen	**Salaam et al 2019, Wood et al 2015**
	3. Availability of medications: Proper pharmacy inventory control and stock delivery has aided in medication adherence	**Miller et al 2017**
ENVIRONMENT (Regulatory, market and policy framework)	**1. NGO Support**: Patients has reported that sharing their concerns and receiving counselling from NGO/ Health officers acted as a facilitator for drug intake	**Tan et al 2017, Wood et al 2015**

Table 4: Thematic framework for summarizing suggestions to improve medication adherence among CVD & DM patients in India

Main theme/Sub-themes	Suggestions to improve medication adherence	Studies
PATIENTS	**1. Peer support groups:** Patients can motivate each other by forming support groups among themselves	**Krishnamoorthy et al 2018**
	2. Digital reminder system: Patient can use digital reminders such as watch, mobile phone to adhere to their drug schedule	**Krishnamoorthy et al 2018, Miller et al 2017**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Social support:** Family members can be educated and asked to provide support by reinforcing compliance, reminding about drug intake, motivating them patients to avoid substance abuse	**Agarwal et al 2019, Dhar et al 2016, Krishnamoorthy et al 2018, Nimesh et al 2019, Wood et al 2015**
	2. Financial support: Family members can provide financial support to cover the cost of medications, travel etc.	**Gupta et al 2019**
	3. Regular training of healthcare workers: Physicians and other healthcare workers involved in prescribing drugs and counselling should undergo regular training on standard treatment protocols	**George et al 2016, Jayanna et al 2019, Miller et al 2017, Patti et al 2020, Satish et al 2019**
	4. Team work approach: Integration of AYUSH, mental health counsellors, physiotherapist and geriatric clinics at primary healthcare level	**George et al 2016, Miller et al 2017, Patti et al 2020**
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Innovations in patient care:** Healthcare workers can make innovations like dedicated day for specific conditions (diabetes day, etc), dedicated counselling station/session with additional staff for detailing the importance of adherence and complications related to non-adherence, unique pill dispensing mechanism (colour coding)	**Agarwal et al 2019, Dhar et al 2016, Jayanna et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Newtonraj et al 2017, Patti et al 2020, Satish et al 2019, Venkatesan et al 2018, Wood et al 2015**
	2. IEC/BCC/Awareness campaigns: Putting up of IEC materials and conducting campaigns on importance of adherence in public places and workplaces	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Krishnamoorthy et al 2018, Newtonraj et al 2017, Patti et al 2020, Rani et al 2019**
	3. Digitalizing patient treatment record: Digitalizing a dedicated treatment record for each patient can help in better follow-up of the patient and improve adherence	**Jayanna et al 2019, Miller et al 2017, Patti et al 2020, Satish et al 2019, Wood et al 2015**
	4. Polypills: Disseminating the advantages of polypills to healthcare professionals by CME/conferences and patients by public education campaigns; Integration of polypills into clinical practice. etc	**Salaam et al 2019, Wood et al 2015**
ENVIRONMENT (Regulatory, market and policy framework)	**1. Linkage of health services with NGO and community-based organizations:** Community members, volunteers, anganwadi workers, self-help groups and NGO workers can be trained in counselling the patients to improve medication adherence	**Dhar et al 2016, Jayanna et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Miller et al 2017, Tan et al 2017**



141x246mm (72 x 72 DPI)

Supplementary Table 1 Search strategy

Key word	Alternative word
Qualitative studies	((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms] Case studies OR Focused group discussions OR phenomenological studies OR ethnographic studies OR interviews))
Medication Adherence	((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms])
Barriers, Facilitators and solutions	Challenges OR Challenge OR Problem OR Problems barriers OR Difficulties OR Issues OR Limitations OR Obstacles OR Facilitators OR Suggestions OR Solutions
Diabetes mellitus and CVDs	((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms] OR Coronary Disease[MeSH Terms] OR Coronary Artery Disease[MeSH Terms] OR Heart Diseases[MeSH Terms] OR Cerebrovascular Diseases[MeSH Terms] OR Stroke[MeSH Terms]))

India	(India[MeSH Terms] OR Republic of India[MeSH Terms]))

Search results (PubMed):

((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms])) AND ((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms]) OR Life Change Events[MeSH Terms]) OR Trust[MeSH Terms])))) AND ((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms])) AND (India[MeSH Terms] OR Republic of India[MeSH Terms])) – 199 (Filters: Years between 2010 and 2020 and English language publication)

((((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms] Case studies OR Focused group discussions OR phenomenological studies OR ethnographic studies OR interviews))) AND ((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms]))) AND (Challenges OR Challenge OR Problem OR Problems barriers OR Difficulties OR Issues OR Limitations OR Obstacles OR Facilitators OR Suggestions OR Solutions)) AND (((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms] OR Coronary Disease[MeSH Terms] OR Coronary Artery Disease[MeSH Terms] OR Heart Diseases[MeSH Terms] OR Cerebrovascular Diseases[MeSH Terms] OR Stroke[MeSH Terms]))))) AND ((India[MeSH Terms] OR Republic of India[MeSH Terms]))) – 31 results (Filters: Years between 2010 and 2020 and English language publication)

Google scholar: 635 + 22 + 6 + 12 = 675

ScienceDirect: (Diabetes Mellitus OR Cardiovascular Diseases OR Hypertension) AND (Qualitative Study OR Qualitative) AND (India) AND (Adherence) – 238 articles

Cochrane library: (Diabetes Mellitus OR Cardiovascular Diseases OR Hypertension) AND (Qualitative Study OR Qualitative) AND (India) AND (Adherence) – 34 articles

BMJ Open

Patient and Provider's perspective on barriers and facilitators for medication adherence among adult patients with Cardiovascular Diseases and Diabetes Mellitus in India – A qualitative evidence synthesis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055226.R1
Article Type:	Original research
Date Submitted by the Author:	10-Dec-2021
Complete List of Authors:	Krishnamoorthy, Yuvaraj; JIPMER PSM, Rajaa, Sathish; Jawaharlal Institute of Postgraduate Medical Education, Rehman, Tanveer; PGIMER Thulasingam, Mahalakshmi ; JIPMER, Department of Preventive and Social Medicine
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Cardiovascular medicine, Diabetes and endocrinology
Keywords:	QUALITATIVE RESEARCH, PREVENTIVE MEDICINE, PRIMARY CARE, Coronary heart disease < CARDIOLOGY, DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Patient and Provider's perspective on barriers and facilitators for medication adherence among adult patients with Cardiovascular Diseases and Diabetes Mellitus in India – A qualitative evidence synthesis

Running head: Barriers and facilitators for medication adherence among CVD and DM patients in India

Article category: Systematic Review

Yuvaraj Krishnamoorthy[1], Sathish Rajaa[2], Tanveer Rehman[3], Mahalakshmy Thulasingam[4]

[1]Assistant Professor, Department of Community Medicine, ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India;

Contact Number: +91 9551892665

Email id: yuvi.1130@gmail.com

[2]Assistant Professor, Department of Community Medicine, ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India;

Contact Number: +91 9791974633

Email id: psrajaa2410@gmail.com

[3]Independent Author, Kolkata, West Bengal, India

Contact Number: +91 8336922482

Email id: drtanveerrehman@gmail.com

[4]Associate Professor, Department of Preventive and Social Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry - 605006, India;

Contact Number: +91 9488729774

Email id: mahalakshmi.dr@gmail.com

Corresponding Author:

Dr Sathish Rajaa,

Assistant Professor,

Department of Community Medicine,

ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India

Contact Number: +91 9791974633

Email id: psrajaa2410@gmail.com

Key messages:

- This is the first review exploring factors associated with drug adherence among CVD & DM patients in India
- Patient-related barriers were lack of knowledge about their condition, forgetfulness, stigma and stress
- Care team-related barriers waere lack of family support, risk communication and physician attitude
- Health system-related barriers were accessibility, affordability, availability and acceptability
- Solutions to address these barriers were peer support group, digital reminders and innovations in patient care

Abstract:

Objective:

To explore the various stakeholders' perspectives on barriers and facilitators for medication adherence among CVD and DM patients in India.

Methods:

A comprehensive systematic search was conducted in Medline, Cochrane library, Science Direct and Google Scholar from January 2010 to July 2020. We used the framework of the systems approach for healthcare delivery to conduct thematic analysis, using published qualitative literature to derive relevant themes, sub-themes and codes.

Setting: A Qualitative Evidence Synthesis of qualitative published studies from India

Subjects: A Qualitative Evidence Synthesis of the available qualitative evidence on the barriers and facilitating factors for medication adherence among CVD and DM patients in India

Results:

In total, 18 studies were included. Major barriers reported were lack of understanding about the disease, complications related to non-adherence, followed by forgetfulness, lack of family support and risk communication. Health system-related barriers such as accessibility, affordability, and acceptability were also reported by majority of the studies. Creation of peer support group, digital reminder system, integration of AYUSH, mental health, physiotherapy and geriatric clinics at primary healthcare level and innovations in patient care were suggested to counter these barriers in medication adherence.

Conclusion:

Such patient-specific targeted interventions needs to be developed to achieve better control among CVD and DM patients.

Keywords: Cardiovascular Diseases, Diabetes Mellitus, Medication Adherence, Qualitative Research

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality globally and in India.[1,2] More than a quarter (28%) of all deaths in India are attributable to CVDs with Ischemic heart disease (IHD) and stroke constituting the majority (83%).[3] On the other hand, India ranks second after China in the global diabetes epidemic, with a prevalence of around 10%.[4] Both diabetes mellitus (DM) and hypertension have long been recognized as independent risk factors for CVDs, whereas adherence to prescribed hypoglycaemic and antihypertensive drug therapies have significantly reduced the risk.[5-8] At least half of hypertensive & DM patients stop taking their medication within a year, often without informing their provider. With further non adherence and attrition over time, medication adherence has emerged as a significant public health priority.[9]

Medication adherence is defined as the extent to which a person's behaviour coincides with the agreed medication regimen or health advice from a health care provider.[10] It has three components: initiation (when the patient takes the first dose of prescribed medication), implementation (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen), and discontinuation (when no more doses are taken after that).[11] Medication adherence is of growing interest to clinicians, healthcare systems, and other stakeholders (e.g., payers). There is soaring evidence that establishes nonadherence is often associated with lower quality of life, adverse clinical events, increased need for medical interventions, mortality, and thus giving rise to avoidable out-of-pocket expenditure in health.[12] Non-adherent hypertensive and stable coronary heart disease (CHD) patients have a four to five times higher risk of developing CHD and death, when compared to adherent patients.[13,14] Similarly, the likelihood of hospitalization is doubled among DM & hypertensive patients who are non-adherent to prescribed therapies compared to the general population. Despite recent advancements in pharmacologic treatment and technology to treat and monitor DM and CVD patients,

medication adherence is of particular concern in low-and-middle-income countries (LMIC) like India, where accessibility and affordability are still issues.[3,15]

Barriers to adherence can be comprehended as the patient, medication, provider, and health system factors, with interactions among them.[16,17] Patient factors that influence adherence include poor health literacy, cultural beliefs regarding medication effectiveness, and religious healing practices.[17] Low income, forgetting to take medication, and perceptions regarding pills like safety concerns, convenience, and necessity add to the above list.[16,17] Inadequate knowledge about a drug and its use, not being convinced of the need for medication, fear of adverse effects, and long-term treatment regimens also prompt medication discontinuation.[15] Clinician factors cover failure to recognize nonadherence, prescription of complex and multidrug regimens, ineffective communication of benefits of medications, and excluding patients in the treatment decision–making process.[17] Health system factors comprise limited insurance coverage, poor coordination of care between inpatient and outpatient settings, and inadequate communication between prescribers (i.e., specialists and primary care clinicians). In addition, the caregivers' aspect also becomes relevant in determining patients' adherence as CVD patients with a caregiver are more likely to be adherent to medications.[18] Hence identifying specific barriers for each patient and adopting suitable techniques to overcome them is imperative to improve medication adherence. Some of the facilitators successful in overcoming these barriers include a personal medication counsellor in the care continuum to guide patients with medication use, single-pill fixed-dose combinations, training pharmacists as coaches for drug therapies, building peer groups for chronic conditions, and developing information systems in the follow-up of patients.[19]

Quantitative studies have focused on medication adherence incidence, and identification of its potential risk factors. They do not, however, uncover life circumstances that may influence adherence from the patient perspective. The inclusion of qualitative studies in our review will

provide a better understanding of the barriers and facilitators from the perspective and experiences of patients, healthcare providers, and caregivers.[20] Qualitative evidence synthesis, a novel research method, brings together the available qualitative evidence from primary studies through a systematic review process. Despite the evidence obtained from primary qualitative studies could be conceptually richer, a qualitative evidence synthesis can aid us in getting an overall view of the findings, and help us in addressing subtle and sensitive issues that most primary studies encounter. The findings from a qualitative evidence synthesis can guide us in crucial making policy recommendations in health care, retaining the impact of individual studies and group experiences. [21] Therefore, the current review was done to understand the perspective of various stakeholders (patients, caregivers, and healthcare providers) on the barriers and facilitators for medication adherence among CVD and DM patients in India. We also explored the suggestions and solutions provided by these stakeholders in overcoming the reported barriers.

METHODS

This review was performed by adhering to the "enhancing transparency in reporting the synthesis of qualitative research (ENTREQ)" statement.[22] We registered our protocol in the PROSPERO database (Registration number - CRD42020199529). We also searched PROSPERO and Cochrane to ensure that no similar review protocol has been reported. We also performed a preliminary search to ensure that no previous reviews of our similar topic targeting the Indian population were published.

Study design

We performed an evidence synthesis of the available qualitative evidence on the barriers and facilitating factors for medication adherence among CVD and DM patients. This review would

help to aggregate the evidence of peer-reviewed articles in this field and build an organized empirical research outline based on prior knowledge.

Eligibility criteria

Study type

We have included qualitative peer-reviewed studies conducted in India for our current review. Furthermore, qualitative evidence from other mixed methods studies was screened for eligibility and included in the qualitative component was relevant to our review. In addition, we included studies using qualitative techniques for data collection such as focussed group discussion (FGD), in-depth interviews (IDI), and Key Informant Interviews (KII).

Participant type

We have included the studies reporting the barriers and facilitators of medication adherence from patients' perspectives (CVD and DM), family members, healthcare workers (HCWs), or health system policymakers in India. HCWs were defined as per WHO recommendation as "all the persons involved in the actions whose primary intent is to enhance the health."[23]

Outcome

The phenomenon of interest in our review was to explore the barriers and facilitators for medication adherence among CVD and DM patients in India. We also explored the possible suggestions and solutions to address the barriers and improve compliance, as experienced by the patients, caregivers, family members, HCWs, and other relevant stakeholders.

Exclusion criteria

We have excluded the studies not available in English, books or conference abstracts or grey literature, or editorial comments. We have also excluded the studies reporting only quantitative data such as cross-sectional surveys, case-control, cohort studies, or intervention trials.

Search strategy

We have conducted a comprehensive and systematic search in databases and search engines such as Medline, Cochrane library, ScienceDirect, and Google Scholar. A combination of medical subject heading (MeSH) and free-full text terms were used for carrying out a literature search. The detailed search strategy and search results in the databases mentioned above and search engines are provided in Supplementary File 1. In addition to this, we also checked the reference list of primary studies obtained via electronic search and included articles relevant to our review and analysis. The search was conducted in all the databases from January 2010 to July 2020 with English language restriction for publication. Furthermore, the search timeline was restricted to ensure that our work provides a broader view and identifies the emerging issues.

Study selection process

Two investigators (YK and TR) independently performed the literature search, screened the title and abstract of all the identified studies, and retrieved the full text for articles relevant to our review. Further full-text screening of the retrieved articles was done again independently by the two investigators (YK, TR) to select the studies matching the eligibility criteria of our review. Disagreements during this process between the two investigators were resolved through consultation with a third investigator (SR).

Data Extraction and Management

After the study selection, two investigators (YK and TR) independently extracted the relevant data and study characteristics onto a predetermined data extraction format. Data entry was double-checked for accuracy by a third investigator (SR) by comparing the data presented in the review and individual study reports. As a result, we have extracted the following study characteristics: general information such as the name of the first author, the country in which the study was done, and year of publication, in the methods section, data collection period, study design, study participants, sample size, sampling technique, and data collection

procedure. In addition, barriers, facilitators, suggestions, and solutions to medication adherence were identified systematically.

Quality assessment

Two investigators (YK and SR) independently performed the quality check using the Critical Appraisal Skills Programme (CASP) criteria.[24] This checklist has been widely used for assessing the quality of studies included in this Qualitative Evidence synthesis.[25] This has helped determine whether the studies included are coherent with the quality appraisal standard for qualitative studies. This checklist consists of 10 questions concerning the study's clarity, methodology, and results to rank the included studies. Subsequently, these studies were stratified into high quality (three stars for studies scoring 8 to 10 points), medium quality (two stars for studies scoring 4 to 7 points), and low rate (one star for studies scoring 0 to 3 points). We did not exclude the low-quality studies, but the interpretation of results was made with caution. Disagreements during the quality assessment process were resolved by discussion with the third investigator (TR).

Data Analysis

We analysed and reported the findings in separate clusters such as patients, caregivers, family members, HCWs, and policymakers to demonstrate the differences among these subgroups. We have adopted a thematic framework analysis to analyse and synthesize the data. Thematic framework analysis has been helpful as the evidence was primarily descriptive and improved our understanding of the barriers and facilitators in medication adherence among CVD and DM patients. This framework synthesis has five stages of synthesizing the qualitative data.

First stage - Familiarisation with the data: Primary investigator (YK) did the process of familiarisation with data by reviewing all the selected articles against the objective of our review and found the recurrent themes across the included studies.

The second stage - Identifying the thematic framework: The investigators used a predetermined thematic framework developed using literature to guide the thematic analysis. The final framework comprised of a detailed list of facilitators and barriers for medication adherence and also solutions to address the issue.

Third stage - Indexing: Two independent investigators (YK and SR) read the extracted information and searched for themes as per the predetermined thematic framework and found additional emerging themes. The framework underwent several revisions as and when a new theme emerged. This has been performed through discussion and agreement between the entire team of investigators. Next, all the studies were completely read and examined till there was no new emergent theme. Coding of the data was then done as per the themes identified in our analysis. Finally, each preliminary study indexing was done using the codes related to the thematic framework. Whenever appropriate, sections of the studies were indexed with one or more codes.

Fourth stage - Charting: The investigators have sorted the data based on the themes and presented these themes in the tabular format (chart). The rows and columns of the table indicate the themes related to the studies, which enabled us to compare the study findings across various themes and subthemes.

***Fifth stage - Mapping and interpretation*:** The investigators used these charts to define the concepts identified, and mapped the nature and range of the phenomena. Our review explored the associations between the various themes and helped in clarifying the findings. Finally, we mapped and interpreted the findings in line with our objectives and emergent themes.

Results

Study selection

A comprehensive and systematic search was done to identify the relevant studies from January 2010 to July 2020. In total, we identified 1187 citations, and after the removal of duplicates from multiple databases, 982 records were screened for their title and abstract and assessed for eligibility. From these records, we retrieved 33 articles, and after going through the full text of these articles, 18 studies were included in the review. (**Figure 1**).[26-43]

Characteristics of the studies included

Characteristics of the included studies are reported in **Table 1**. Of the 18 studies included, 9 (50%) were from the Southern region, followed by 7 (38%) from the Northern part of India. The mean age of the participants ranged from 25-76 years. The typology of the studies comprised of in-depth interviews (IDIs) and focussed group discussions (FGDs). The study participants were primarily patients with diabetes, hypertension, or any cardiovascular diseases (to explore the patient perspective), and health care workers (4 studies) providing care to them (to obtain the provider perspective). The total sample size of the included studies ranged from 6 to 100. The majority (10 of the included studies) were done in a community setting, while the rest were either facility-based or had participants from ongoing trials. Four of the included studies used software for analysing the qualitative data, while the rest followed manual methods. Most of the included studies (14 out of 18) had higher ratings indicating high-quality evidence.

Narrative synthesis

Significant findings from the review showed that factors contributory to adherence come under three themes: patient-related, family-related, and health system-related factors. The barriers, facilitators, and suggestions to improve medication adherence were summarized under these three themes.

Barriers in medication adherence

Table-2 shows the thematic framework analysis related to barriers in medication adherence among CVD and DM patients. All the 18 included studies have explored and reported on these barriers.

Patient-related factors

Significant patient-related barriers (10 studies) reported were lack of knowledge or understanding about the disease, its complications related to nonadherence, and the treatment schedule, followed by forgetfulness to take medicine (7 studies). Reasons provided for the same were the patients' busy schedule, laziness, or forgetting to take the medication while traveling out-of-station. Patients have also reported certain misconceptions about the medicines like the risk of long-term neurological illness because of medication intake, inferior quality of drugs provided in hospitals, and wrong perception about stopping the medications once the patient feels normal. Patients in some studies have reported that they practice alternate systems of medicine such as herbal medicines and avoid taking allopathic medicines leading to poorer control of their condition. Substance use such as alcohol or tobacco use, side effects related to drugs, stress, and stigma were reported to be other barriers

Family-related factors

The patients and providers have reported a lack of family support as a significant contributing factor for nonadherence. In addition, the lack of social and emotional support to the patients further contributes to the nonadherence among the patients suffering from CVDs and DM. Domestic works, personal priorities, commitments, or other issues hinder the family members from providing the above-mentioned support to the patients.

Health system-related factors

In most of these studies, providers were also interviewed to understand the factors related to the health system responsible for nonadherence among CVD and DM patients. Healthcare providers and patients interviewed, in almost all these studies, have reported affordability,

accessibility, and acceptability as the major factors hindering medication adherence. Affordability is an issue with patients seeking healthcare in private facilities and patients getting care in public healthcare facilities. Though there was no direct medical cost related to government hospitals or primary healthcare centres, direct non-medical costs such as transport (due to poor accessibility) and indirect costs such as loss of wages (due to inconvenient consultation timing) were higher amongst these patients. In addition, patients have a wrong perception that medications in public facilities are of poorer quality, making them choose private health facilities, including those belonging to lower socioeconomic status. Lack of risk communication, counselling, or empathy by the physicians mainly due to overburdening public health facilities and time constraints were the other health system-related barriers reported by the providers and patients.

Facilitators in medication adherence

Facilitators in medication adherence were also summarized using the pre-existing thematic framework (**Table-3**). In total, ten studies have explored the facilitators in medication adherence from the patient or providers' perspective.

Patient-related factors

Most of the studies (5 studies) reported fear of complications due to nonadherence and self-perception of being healthy (once they adhere to the medications) as the significant facilitators. In addition, having a reminder system in the form of a reminder notebook, separate pillboxes/cases/covers or personalized shelf facilitate the patients in adhering to the medications. Some studies have also reported that integrating drug intake into daily routine activities and peer influence acts as a good facilitator in compliance with medications.

Family-related factors

Family support was reported as a major facilitating factor for compliance with medication. Apart from the support, adverse experiences in the past, such as death or severe complications

among the family members, instilled fear in the patients, making them more compliant to the medications.

Health system-related factors

Barriers reported in some of the studies, such as empathy and counselling by healthcare providers, were considered facilitators by the other studies' patients. Another major facilitator from the health system side is the trust that patient has in their physician and their willingness to effectively follow advice related to self-care and adherence. Other familiar facilitators reported by the patients and providers were the use of dedicated pill cover/boxes for each drug provided in the clinic, linkage of health services with NGO for provision of counselling and generating awareness, availability of medication, and use of polypills.

Suggestions to improve medication adherence

Suggestions and solutions to enhance the compliance to medication were reported in 16 out of the 18 included studies based on either patient or provider's perspective (**Table-4**). Few suggestions were related to patients and family members, while the majority were related to the change in the health system.

Patient and family-related factors

Creating or joining a peer support group was one of the major suggestions related to the patients. This will help by motivating the patients to be more compliant with medications and other self-care practices. Digital reminder systems using a watch and a mobile phone can also improve medication adherence.

Health system-related factors

Innovations in patient care, have been necessitated as an important factor to promote drug adherence. Some of the innovations suggested were dedicated days for specific disease conditions to avoid overburdening the facilities, a dedicated counselling station for drug adherence during the clinic with separate human resource, and a unique pill dispensing

mechanism like colour coding, etc. In addition, Information Education and Communication (IEC)/Behaviour change communication (BCC) campaigns, digitalizing the patient treatment records, linkage of healthcare services with NGOs or community-based organizations, regular training of healthcare workers, and promotion of polypill use were other common suggestions offered by the healthcare providers.

Discussion

We conducted this review to integrate the qualitative evidence on barriers and facilitators for medication adherence among CVD and DM patients in India. We also further explored the suggestions to improve the same. The studies included in our review involved a total of 636 participants (534 CVD and DM patients, 102 healthcare providers). The majority of the included studies were of high quality with respect to study clarity, methodology and results. We summarized under three major themes: barriers, facilitators, suggestions and reported the findings under the following four sub-themes: patients, care team, healthcare organization and environment-related factors.

Comparison of findings with previous literature

Barriers in medication adherence

Major barriers were lack of patient's understanding about the disease and its complications, forgetfulness and misconception about the medications. Lack of family support was seen as a major barrier from both patient's and provider's perspectives. In addition to these factors, stress and stigma were also mentioned as important factors among patients to not take medicine on time. In addition to the above, medication adherence could also be highly hindered by the patients' cultural beliefs, perceived discrimination, and social customs, which are highly prevalent in a culturally influenced country like India. A few studies have also shown evidence of improvisation in medication adherence where efforts were taken to overcome the cultural barriers. [44] We also found major health system-related barriers were lack of accessibility and

availability, higher cost of medications and poor physician attitude. These findings were in line with the previous review conducted among South-East Asian DM patients.[44,46] In addition, our findings about patients related factors were found to be similar to other patients belonging to non-English speaking Hispanic, South American ethnic groups, as they also had misconceptions related to therapy, lack of understanding about their condition, with additional stress and stigma as a factor for non-adherence.[47-49]

Facilitators in medication adherence

Fear of complications, self-perception of being healthy, having a reminder system were reported as major facilitators by patients. Physician trust, advice, empathy, and counselling were the other provider-related facilitators in adhering to medications. Common facilitators as reported by the patients and providers were: dedicated pill cover/boxes for each drug provided in the clinic, availability of medication and use of polypills. These findings were also in line with the previous qualitative reviews conducted in low middle-income countries including India.[47-50]

Suggestions to improve medication adherence

The solutions provided by the patients and health professionals were in line with the barriers identified in our review. Proper physician counselling to make the patients understand their own condition, complications of the disease and avoid misconception about the drugs and their side effects, good family support, making the medication accessible and available free of cost were suggested as major suggestions to improve medication adherence. Similar interventions were also suggested by previous qualitative evidence on medication adherence among CVD and DM patients.[45-49] It is also interesting to note that medication adherence is also hurdled by the patients' intention towards adherence, and this intention might vary across nations and cultural groups. The patient's intention not to refill prescriptions due to cost, not to take medication because the patient feels better, also influence the patient's decision. Thus future

research exploring these reasons on patient's choice to adhere or not, rather than an inability to adhere (e.g., forgetting, no access) needs to be encouraged.

Strengths and limitations of the study

To the best of our knowledge, this is the first review exploring and synthesizing the qualitative factors associated with medication adherence among CVD and DM patients in India. We have provided comprehensive and systematic evidence on the barriers, facilitators related to medication adherence, adhering to the ENTREQ statement and ensuring transparency and reproducibility. We examined this evidence through the lenses of a well-established theoretical framework model. Moreover, our study was able to provide valuable suggestions to promote medication adherence from both patients and provider's perspectives. In addition to these strengths, we found that the highest-rated studies contributed to the majority of the factors found in our review. This in turn ensures the transferability (external validity) of our review findings.

However, our review has certain limitations. We did not search grey literature, possibly missing some insights for our review. Hence, we cannot rule out of the dissemination bias with respect to accurate and complete representation of the phenomenon of interest. We focussed primarily on the patient and provider perspective on medication adherence.[51] Hence, we cannot comment on the organizational or political influences on the adherence to long-term therapies as mentioned in the WHO report.[16] The sample size of the included studies can be considered relatively low (median sample size - 30). However, all the studies were conducted till the achievement of data saturation. In addition to the above, these results and suggestions need to be considered after taking into account India's cross-cultural adaptations, customs, linguistic variations and genetic susceptibility and higher prevalence of risk factor profile.

Implications for clinical and public health practice

Improving medication adherence is essential to achieve better control and prevent life-threatening complications. Factors related to patients such as self-awareness and fear about the condition and its complications acted as a major facilitator for medication adherence. We also found more modifiable barriers related to medication intakes such as forgetfulness, lack of knowledge, and misconception about medications. Interventions should focus on these modifiable barriers such as knowledge barriers, intention barriers and health system-related barriers to achieve better adherence. In addition, it is important for the family members to help the patients in mapping their daily routine and link the medicine intake with these routines to facilitate adherence. Our review also suggested that healthcare providers play an important role in promoting medication adherence. Hence, the interventions should not only target the patients but also the family members and healthcare providers and they should be tailored to suit differences in setting, culture and type of the patients.

Implications for future research

More evidence need to be generated with respect to the solutions obtained in our review such as memory tools including the digital solutions, polypills, peer support groups etc. Further qualitative studies including the subgroup of patients with CVD and DM under different stages and treatment regimens are required to contextualize the medication adherence. Exploring the barriers using a theoretical framework with the same methodological approach, can provide more reliable evidence to develop patient-centred interventions and achieve better control among CVD and DM patients.

Conclusion:

In our review, we categorised the facilitating factors and barriers influencing medication adherence into patient related, health system related and care team related factors. Thus, we advocate creation of peer support group, use of digital reminder system for overcoming patients related factors, and integration of AYUSH services, mental health, physiotherapy and geriatric

clinics even at the primary healthcare level for overcoming the health system related barriers towards medication adherence.

References:

1. Walker IF, Garbe F, Wright J, Newell I, Athiraman N, Khan N, et al. The Economic Costs of Cardiovascular Disease, Diabetes Mellitus, and Associated Complications in South Asia: A Systematic Review. Value Health Reg Issues. 2018;15:12–26.
2. Glovaci D, Fan W, Wong ND. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. Curr Cardiol Rep. 2019;21:21.
3. Prabhakaran D, Jeemon P, Sharma M, Roth GA, Johnson C, Harikrishnan S, et al. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018;6:e1339–51.
4. Tandon N, Anjana RM, Mohan V, Kaur T, Afshin A, Ong K, et al. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018;6:e1352–62.
5. Durand H, Hayes P, Morrissey EC, Newell J, Casey M, Murphy AW, et al. Medication adherence among patients with apparent treatment-resistant hypertension: systematic review and meta-analysis. J Hypertens. 2017;35:2346–57.
6. Polypharmacy and Medication Adherence in Patients With Type 2 Diabetes | Diabetes Care [Internet]. [cited 2020 Jul 30]. Available from: https://care.diabetesjournals.org/content/26/5/1408.short
7. Vrijens B, Antoniou S, Burnier M, de la Sierra A, Volpe M. Current Situation of Medication Adherence in Hypertension. Front Pharmacol [Internet]. 2017 [cited 2020 Jul 31];8. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2017.00100/full

8. Rehman T, Rajaa S, Kumar G, Jayalakshmy R. Prevalence and factors influencing diabesity among persons with type 2 diabetes mellitus in urban Puducherry: A cross-sectional analytical study. Indian J Community Med. 2020 Jul;45(3):315.
9. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence. 2016;10:1299–307.
10. Leporini C, De Sarro G, Russo E. Adherence to therapy and adverse drug reactions: is there a link? Expert Opin Drug Saf. 2014;13 Suppl 1:S41-55.
11. Lam WY, Fresco P. Medication Adherence Measures: An Overview. BioMed Res Int. 2015; 2015:1–12.
12. Kvarnström K, Airaksinen M, Liira H. Barriers and facilitators to medication adherence: a qualitative study with general practitioners. BMJ Open. 2018;8:e015332.
13. Ferdinand KC, Senatore FF, Clayton-Jeter H, Cryer DR, Lewin JC, Nasser SA, et al. Improving Medication Adherence in Cardiometabolic Disease. J Am Coll Cardiol. 2017;69:437–51.
14. Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. Adv Ther. 2005;22:313–56.
15. Dennis T, Meera NK, Binny K, Sekhar MS, Kishore G, Sasidharan S. Medication adherence and associated barriers in hypertension management in India. CVD Prev Control. 2011 Jan 1;6(1):9-13.
16. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. Circulation. 1997;95:1085–90.

17. WHO | ADHERENCE TO LONG-TERM THERAPIES: EVIDENCE FOR ACTION [Internet]. WHO. World Health Organization; [cited 2020 Jul 30]. Available from: http://www.who.int/chp/knowledge/publications/adherence_report/en/

18. Aggarwal B, Liao M, Mosca L. Medication Adherence Is Associated with Having a Caregiver Among Cardiac Patients. Ann Behav Med Publ Soc Behav Med. 2013;46:237–42.

19. Daliri S, Bekker CL, Buurman BM, Scholte op Reimer WJM, van den Bemt BJF, Karapinar – Çarkit F. Barriers and facilitators with medication use during the transition from hospital to home: a qualitative study among patients. BMC Health Serv Res. 2019; 19:204.

20. Rathbone AP, Todd A, Jamie K, Bonam M, Banks L, Husband AK. A systematic review and thematic synthesis of patients' experience of medicines adherence. Res Social Admin Pharm. 2017 May 1;13(3):403-39.

21. Flemming K, Booth A, Garside R, Tunçalp Ö, Noyes J. Qualitative evidence synthesis for complex interventions and guideline development: clarification of the purpose, designs and relevant methods. BMJ Global Health. 2019 Jan 1;4(Suppl 1):e000882.

22. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012; 12:181

23. Mohanty A, Kabi A, Mohanty AP. Health problems in healthcare workers: A review. J Family Med Primary Care. 2019 Aug;8(8):2568.

24. Critical Appraisal Skills Programme (2018). CASP (Qualitative) Checklist. [online] Available at: https://casp-uk.net/wp-content/uploads/2018/01/CASP-Qualitative-Checklist-2018.pdf Accessed: 12 September 2020

25. Booth A, Noyes J, Flemming K, Gerhardus A, Wahlster P, van der Wilt GJ,et al. Structured methodology review identified seven (RETREAT) criteria for selecting qualitative evidence synthesis approaches. J Clin Epidemiol. 2018 Jul 1;99:41-52.
26. Agarwal A, Davies D, Goenka S, Prabhakaran D, Huffman MD, Mohanan PP. Facilitators and barriers of heart failure care in Kerala, India: A qualitative analysis of healthcare providers and administrators. Indian Heart J. 2019; 71(3):235–41.
27. Dhar L. Perceptions of global coronary heart disease risk, and adherence to antihypertensive treatment among low income urban women in Delhi, India (Doctoral dissertation, Curtin University).
28. George CE, Ramadas D, Norman G, Mukherjee D, Rao T. Barriers to cardiovascular disease risk reduction: Does physicians' perspective matter? Indian Heart J. 2016; 68(3):278–85
29. Gupta S, Dhamija JP, Mohan I, Gupta R. Qualitative Study of Barriers to Adherence to Antihypertensive Medication among Rural Women in India. Int J Hypertens. 2019; 2019:1–7.
30. Gupta S, Virk A, Mittal A, Agarwal B. Patterns and determinants of healthcare-seeking behavior among hypertensive patients in a rural population of north India: A mixed-method study. J Family Med Prim Care. 2020; 9(6):2830
31. Jayanna K, Swaroop N, Kar A, Ramanaik S, Pati MK, Pujar A, et al. Designing a comprehensive Non-Communicable Diseases (NCD) programme for hypertension and diabetes at primary health care level: evidence and experience from urban Karnataka, South India. BMC Public Health. 2019; 19:1
32. Krishnamoorthy Y, Giriyappa DK, Eliyas SK, Priyan S, Saya GK, Lakshminarayanan S. Patient and Provider's Experience and Perspective in Addressing Barriers to

Medication Adherence Among Noncommunicable Disease Patients in Rural Puducherry, South India—A Qualitative Study. J Patient Exp. 2019; 6(3):216–23

33. Kusuma YS. Migrants' Perceptions on Barriers to Treatment Seeking for Hypertension: A Qualitative Study from Delhi, India. Studies on Ethno-Medicine. 2010; 4(3):173–6
34. Miller V, Nambiar L, Saxena M, Leong D, Banerjee A et al. Exploring the barriers to and facilitators of using evidence-based drugs in the secondary prevention of cardiovascular diseases: findings from a multistakeholder, qualitative analysis. Global Heart. 2018; 13(1):27-34.
35. Newtonraj A, Arun S, Bazroy J, Tovia S. Lay perspectives on causes and complications of hypertension; and barrier to access health care by known hypertensive patients: a qualitative study from a rural area of South India. Int J Community Med Public Health. 2017; 4(3):704
36. Nimesh VV, Halder A, Mitra A, Kumar S, Joshi A, Joshi R, et al. Patterns of healthcare seeking behavior among persons with diabetes in Central India: A mixed method study. J Family Med Prim Care. 2019; 8(2):677.
37. Pati S, Van den Akker M, Schellevis FF, Sahoo K, Burgers JS. Managing diabetes mellitus with comorbidities in primary healthcare facilities: a qualitative study among physicians in Odisha, India. 2020. Research square [preprint] doi: 10.21203/rs.3.rs-22272/v1
38. Anitha Rani M, Shriraam V. Are Patients With Type 2 Diabetes Not Aware or Are They Unable to Practice Self-Care? A Qualitative Study in Rural South India. J Prim Care Community Health. 2019; 10:2150132719865820.
39. Salam A, Praveen D, Patel A, Tewari A, Webster R. Barriers and facilitators to the use of cardiovascular fixed-dose combination medication (polypills) in Andhra Pradesh, India: a mixed-methods study. Global Heart. 2019; 14(3):303-10.

40. Satish P, Khetan A, Barbhaya D, Agarwal M, Mohan SK, Josephson R, Webel AR. A qualitative study of facilitators and barriers to cardiovascular risk factor control in a semiurban population in India. J Family Med Prim Care. 2019; 8(12):3773-3778.
41. Thakur JS, Vijayvergiya R, Jaswal N, Ginsburg A. Assessment and barriers to medication adherence for secondary prevention of cardiovascular disease among patients with coronary artery disease in Chandigarh, India. Int J Non-Commun Dis. 2016;1:37-41.
42. Venkatesan M, Dongre AR, Ganapathy K. A community-based study on diabetes medication nonadherence and its risk factors in rural Tamil Nadu. Indian J Community Med. 2018; 43(2):72-76
43. Wood F, Salam A, Singh K, Day S, Jan S, Prabhakaran D, et al. Process evaluation of the impact and acceptability of a polypill for prevention of cardiovascular disease. BMJ Open. 2015; 5(9):e008018
44. Saha S, Korthuis PT, Cohn JA, Sharp VL, Moore RD, Beach MC. Primary care provider cultural competence and racial disparities in HIV care and outcomes. J Gen Intern Med. 2013;28(5):622-9. https://doi. org/10.1007/s11606-012-2298-8.
45. Sohal T, Sohal P, King-Shier KM, Khan NA. Barriers and Facilitators for Type-2 Diabetes Management in South Asians: A Systematic Review. PLoS ONE. 2015; 10(9): e0136202.
46. Sears K, Scobie A, MacKinnon NJ. Patient-related risk factors for self-reported medication errors in hospital and community settings in 8 countries. Can Pharm J: Revue des Pharmaciens du Canada. 2012 Mar;145(2):88-93.
47. Nam S, Chesla C, Stotts NA, Kroon L, Janson SL. Barriers to diabetes management: patient and provider factors. Diabetes Res Clin Pract. 2011; 93(1):1–9

48. Lipton RB, Losey LM, Giachello A, Mendez J, Girotti MH. Attitudes and issues in treating Latino patients with type 2 diabetes: views of healthcare providers. Diabetes Educ. 1998; 24: 67–71

49. Sridharan SG, Chittem M, Maya S. Patients' Experiences of Barriers and Facilitators for Adherence to Type 2 Diabetes Mellitus: A Meta-Ethnography. Journal of Social Health and Diabetes. 2019 Dec;7(02):61-72.

50. Al Hamid A, Ghaleb M, Aljadhey H, et al. A systematic review of qualitative research on the contributory factors leading to medicine-related problems from the perspectives of adult patients with cardiovascular diseases and diabetes mellitus. BMJ Open 2014; 4:e005992.

51. Toews I, Booth A, Berg RC et al. Further exploration of dissemination bias in qualitative research required to facilitate assessment within qualitative evidence synthesis. J Clin Epidemiol 2017; 88:133–139

Table 1: Characteristics of the studies included (N=18)

S.No	Author and year	State	Data collection method	Study participants	Study setting	Approach	Coding	Theoretical framework used	Method of analysis	Sample size	Mean Age in years	Study quality
1.	Agarwal 2019	Kerala	IDI	Clinical and administrative staff	Facility based	NR	Inductive	NR	Dedoose Software	21	NR	***
2.	Dhar et al 2016	Delhi	IDI	Hypertensive women aged 35-59 years	Community based	NR	Inductive	Yes	Manual content analysis	30	48	***
3.	George et al 2016	Karnataka	IDI	Physicians providing Non communicable disease care	Community based	NR	Inductive	NR	Manual content analysis	36	46	***
4.	Gupta et al 2019	Rajasthan	IDI	Hypertensive women	Facility based	NR	NR	NR	Manual content analysis	30	56	**
5.	Gupta et al 2020	Haryana	IDI	Hypertension patients	Facility based	NR	NR	NR	Manual content analysis	100	38-76	***
6.	Jayanna et al 2019	Karnataka	IDI & FGD	Diabetes and Hypertension patients	Facility based	NR	NR	Yes	Manual content analysis	10 IDI + 20 FGDs	NR	***
7.	Krishnamoorthy et al 2018	Puducherry	IDI & KII	Diabetes and Hypertension patients & Healthcare workers	Community based	NR	Inductive	NR	Manual content analysis	6 IDI + 4 KII	NR	***
8.	Kusuma et al 2010	Delhi	KII & FGD	Recent and Settled Migrants having hypertension inhabited in Delhi	Community based	NR	NR	NR	Manual content analysis	14 (KII) + 20 (FGD)	38 – 50 (KII) & 25 – 40 (FGD)	***
9.	Miller et al 2017	Delhi	IDI	Cardiovascular disease patients	Trial based	Descriptive	NR	NR	Manual content analysis	14	NR	***
10.	Newtonraj et al 2017	Tamil Nadu	Personal interviews	Hypertensive patients	Community based	NR	NR	NR	Manual content analysis	40	NR	**

11.	Nimesh et al 2019	Madhya Pradesh	IDI	Individuals with diabetes	Community based	NR	Inductive	Yes	Manual content analysis	60	52	***
12.	Patti et al 2020	Orissa	IDI	Primary care physicians	Facility based	NR	NR	NR	Manual content analysis	17	40	***
13.	Rani et al 2019	Tamil Nadu	FGD	Individuals with diabetes	Community based	Descriptive	NR	NR	Manual content analysis	50	50	**
14.	Salaam et al 2019	Andhra Pradesh	IDI	Patients with Cardiovascular disease	Community based	NR	NR	Yes	NVivo version 11 software	12	62	***
15.	Satish et al 2019	West Bengal	FGD	Patients with hypertension and/or diabetes	Trial based	NR	NR	Yes	Manual content analysis	70	53	***
16.	Thakur et al 2016	Chandigarh	IDI & FGD	Coronary artery disease patients	Facility based	NR	NR	NR	Manual Thematic analysis	20	NR	*
17.	Venkatesan et al 2018	Tamil Nadu	IDI	Health care workers	Community based	NR	NR	NR	Anthropac software	10	NR	***
18.	Wood et al 2015	Hyderabad and Delhi	IDI	Patients with Cardiovascular diseases	Trial based	NR	NR	Yes	Nvivo software	52	57	***

NR – Not Reported
IDI – In depth Interview
FGD – Focussed Group Discussion
KII – Key informant interview

Table 2: Thematic framework analysis for summarizing barriers in medication adherence experienced by CVD & DM patients in India

Main theme/Sub-themes	Barriers in Medication Adherence	Studies
PATIENTS	1. **Lack of awareness/knowledge:** Lack of knowledge and understanding about the disease, its complications and treatment among the patients	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Newtonraj et al 2017, Patti et al 2020, Tan et al 2017, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	2. Forgetfulness: Patients forget to take medicine because of busy schedule	**Dhar et al 2016, Gupta et al 2019, Gupta et al 2020, Rani et al 2019, Venkatesan et al 2018, Wood et al 2015, Tan et al 2017, Thakur et al 2016**
	3. Misconception about medications: Patient has wrong perception about the medications, especially about its side effects and quality	**George et al 2016, Gupta et al 2020, Patti et al 2020, Rani et al 2019, Salaam et al 2019, Tan et al 2017, Venkatesan et al 2018**
	4. Preference to alternate system of medicine: Patients prefers taking herbal and other alternate system of medicines for their condition	**George et al 2016, Tan et al 2017, Venkatesan et al 2018**
	5. Ill effects of substance abuse: Patients have difficulty in adhering to medications during the bout of tobacco or alcohol consumption	**Jayanna et al 2019, Krishnamoorthy et al 2018**
	6. Effect of side effects: Patients stop their medication once they develop side effects related to the drugs	**Venkatesan et al 2018, Wood et al 2015**
	7. Stress: Patients developing stress due to personal or work-related problems are more non-adherent to medications	**Krishnamoorthy et al 2018**
	8. Stigma: Patients feel stigmatised in revealing their disease status to other family/friends leading to lack of support from them	**Krishnamoorthy et al 2018**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Family support:** Lack of physical, emotional and social support as the family members are pre-occupied with domestic works, crisis, other priorities and commitments	**Dhar et al 2016, George et al 2016, Gupta et al 2020, Krishnamoorthy et al 2018, Kusuma et al 2010, Newtonraj et al 2017, Rani et al 2019, Wood et al 2015**
	2. Risk communication: Poor risk communication or counselling to patients and family members about non-adherence to medication by the treating physicians	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Thakur et al 2016**
	3. Physician attitude: Lack of respect, empathy, communication and attention towards patients bythe treating physicians	**Dhar et al 2016, Gupta et al 2019, Kusuma et al 2010, Jayanna et al 2019**

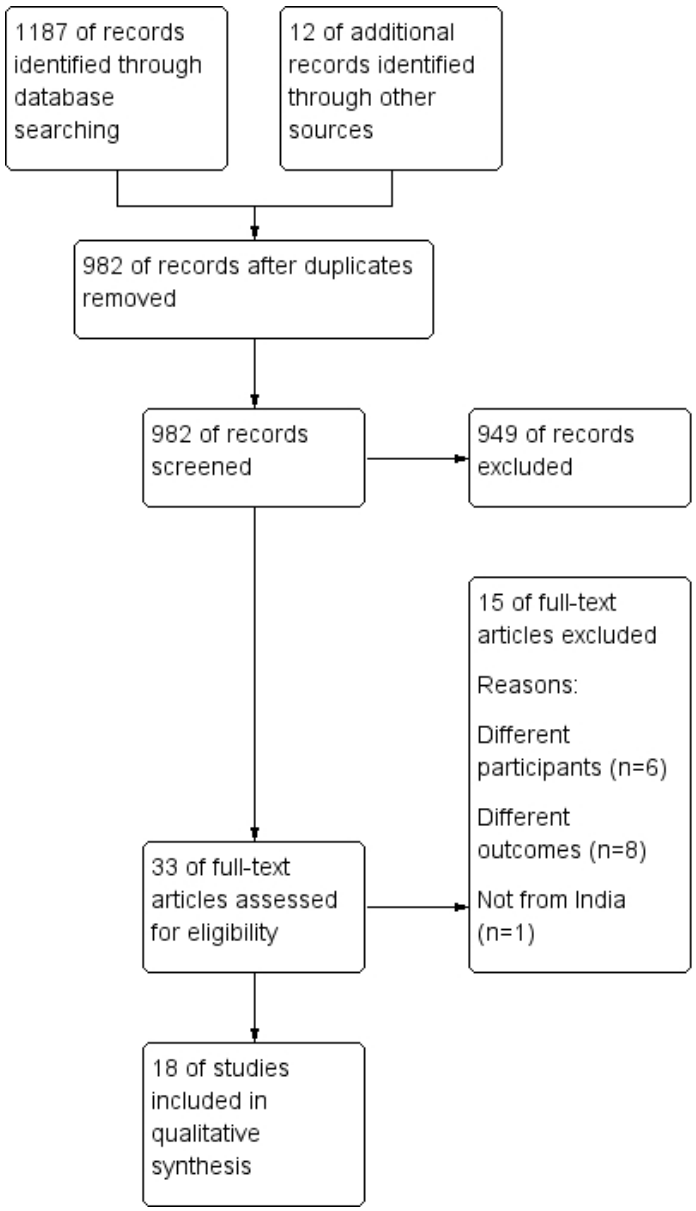
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Affordability:** Patients lose their daily wages due to inconvenient consultation timings in public facilities, which is aggravated by travel costs due to poor access, and higher medication costs while preferring private facilities	**Agarwal et al 2019, Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Kusuma et al 2010, Miller et al 2017, Nimesh et al 2019, Salaam et al 2019, Satish et al 2019, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	2. Accessibility: Lack of access to healthcare facilities (more distance) requiring longer travel and waiting time.	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Miller et al 2017, Newtonraj et al 2017, Tan et al 2017, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	3. Availability: Non-availability of essential medicines in public healthcare facilities	**Dhar et al 2016, Jayanna et al 2019, Kusuma et al 2010, Miller et al 2017, Newtonraj et al 2017, Patti et al 2020, Salaam et al 2019, Wood et al 2015**
	4. Acceptability: Medications from public health facilities are not acceptable to the patients due to poorer quality	
	5. Overburdening of primary health centres: Burdening of primary health facilities lead to time constraints in patient counselling regarding medication adherence	**Jayanna et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Patti et al 2020, Venkatesan et al 2018**

Table 3: Thematic framework for summarizing facilitators in medication adherence experienced by CVD & DM patients in India

Main theme/Sub-themes	Facilitators in Medication Adherence	Studies
PATIENTS	**1. Self-awareness and fear:** Patient's understanding about medicine adherence and fear about complications of non-adherence keeps them healthy	**Krishnamoorthy et al 2018, Miller et al 2017, Patti et al 2020, Satish et al 2019, Tan et al 2017, Wood et al 2015**
	2. Medicine Reminder system: Separate pill boxes/cases/covers, personalized shelf, and maintaining drug record notebook helps them in remembering daily doses	**Dhar et al 2016, Krishnamoorthy et al 2018, Miller et al 2017, Tan et al 2017**
	3. Integrating drug intake with the daily routine: Fixed time for medicine intake, separate place for keeping drug, and making arrangements during travel helps them in adherence	**Dhar et al 2016, Krishnamoorthy et al 2018**
	4. Positive peer influence: Good adherence to medication by the patient's peers motivates the patient to be compliance to their own drug intake	**Gupta et al 2019, Krishnamoorthy et al 2018**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Family support**: Constant reminders by family members for drug intake	**Dhar et al 2016, Gupta et al 2020, Krishnamoorthy et al 2018, Miller et al 2017, Wood et al 2015**
	2. Past adverse experiences: Death of patients' own family members due to complications of the condition has motivated them to adhere to medication	**Dhar et al 2016, Krishnamoorthy et al 2018**
	3. Healthcare provider counselling and empathy: Patients described that counselling from their healthcare providers has motivated them to remain adherent	**Kusuma et al 2010, Miller et al 2017, Patti et al 2020, Salaam et al 2019, Tan et al 2017**
	4. Trust in physician: Adherence is more when a positive rapport and trust is established between the patient and health care providers.	**Dhar et al 2016, Krishnamoorthy et al 2018, Satish et al 2019**
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Dedicated pill boxes/covers:** Provision of different medications in separate boxes/covers in the healthcare facility has helped as the patient to remember which medication to take at what time	**Krishnamoorthy et al 2018, Wood et al 2015**
	2. Combination drugs (polypills): Polypills had the following advantages to facilitate the medication adherence: a smaller number of pills, lower frequency, less chance of forgetting, potential for lower cost, and convenient simpler regimen	**Salaam et al 2019, Wood et al 2015**
	3. Availability of medications: Proper pharmacy inventory control and stock delivery has aided in medication adherence	**Miller et al 2017**
ENVIRONMENT (Regulatory, market and policy framework)	**1. NGO Support**: Patients has reported that sharing their concerns and receiving counselling from NGO/ Health officers acted as a facilitator for drug intake	**Tan et al 2017, Wood et al 2015**

Table 4: Thematic framework for summarizing suggestions to improve medication adherence among CVD & DM patients in India

Main theme/Sub-themes	Suggestions to improve medication adherence	Studies
PATIENTS	**1. Peer support groups:** Patients can motivate each other by forming support groups among themselves	**Krishnamoorthy et al 2018**
	2. Digital reminder system: Patient can use digital reminders such as watch, mobile phone to adhere to their drug schedule	**Krishnamoorthy et al 2018, Miller et al 2017**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Social support:** Family members can be educated and asked to provide support by reinforcing compliance, reminding about drug intake, motivating them patients to avoid substance abuse	**Agarwal et al 2019, Dhar et al 2016, Krishnamoorthy et al 2018, Nimesh et al 2019, Wood et al 2015**
	2. Financial support: Family members can provide financial support to cover the cost of medications, travel etc.	**Gupta et al 2019**
	3. Regular training of healthcare workers: Physicians and other healthcare workers involved in prescribing drugs and counselling should undergo regular training on standard treatment protocols	**George et al 2016, Jayanna et al 2019, Miller et al 2017, Patti et al 2020, Satish et al 2019**
	4. Team work approach: Integration of AYUSH, mental health counsellors, physiotherapist and geriatric clinics at primary healthcare level	**George et al 2016, Miller et al 2017, Patti et al 2020**
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Innovations in patient care:** Healthcare workers can make innovations like dedicated day for specific conditions (diabetes day, etc), dedicated counselling station/session with additional staff for detailing the importance of adherence and complications related to non-adherence, unique pill dispensing mechanism (colour coding)	**Agarwal et al 2019, Dhar et al 2016, Jayanna et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Newtonraj et al 2017, Patti et al 2020, Satish et al 2019, Venkatesan et al 2018, Wood et al 2015**
	2. IEC/BCC/Awareness campaigns: Putting up of IEC materials and conducting campaigns on importance of adherence in public places and workplaces	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Krishnamoorthy et al 2018, Newtonraj et al 2017, Patti et al 2020, Rani et al 2019**
	3. Digitalizing patient treatment record: Digitalizing a dedicated treatment record for each patient can help in better follow-up of the patient and improve adherence	**Jayanna et al 2019, Miller et al 2017, Patti et al 2020, Satish et al 2019, Wood et al 2015**
	4. Polypills: Disseminating the advantages of polypills to healthcare professionals by CME/conferences and patients by public education campaigns; Integration of polypills into clinical practice. etc	**Salaam et al 2019, Wood et al 2015**
ENVIRONMENT (Regulatory, market and policy framework)	**1. Linkage of health services with NGO and community-based organizations:** Community members, volunteers, anganwadi workers, self-help groups and NGO workers can be trained in counselling the patients to improve medication adherence	**Dhar et al 2016, Jayanna et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Miller et al 2017, Tan et al 2017**



141x246mm (72 x 72 DPI)

Supplementary Table 1 Search strategy

Key word	Alternative word
Qualitative studies	((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms] Case studies OR Focused group discussions OR phenomenological studies OR ethnographic studies OR interviews))
Medication Adherence	((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms])
Barriers, Facilitators and solutions	Challenges OR Challenge OR Problem OR Problems barriers OR Difficulties OR Issues OR Limitations OR Obstacles OR Facilitators OR Suggestions OR Solutions
Diabetes mellitus and CVDs	((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms] OR Coronary Disease[MeSH Terms] OR Coronary Artery Disease[MeSH Terms] OR Heart Diseases[MeSH Terms] OR Cerebrovascular Diseases[MeSH Terms] OR Stroke[MeSH Terms]))

India	(India[MeSH Terms] OR Republic of India[MeSH Terms]))

Search results (PubMed):

((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms])) AND ((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms]) OR Life Change Events[MeSH Terms]) OR Trust[MeSH Terms]))) AND ((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms])) AND (India[MeSH Terms] OR Republic of India[MeSH Terms])) – 199 (Filters: Years between 2010 and 2020 and English language publication)

((((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms] Case studies OR Focused group discussions OR phenomenological studies OR ethnographic studies OR interviews))) AND ((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms]))) AND (Challenges OR Challenge OR Problem OR Problems barriers OR Difficulties OR Issues OR Limitations OR Obstacles OR Facilitators OR Suggestions OR Solutions)) AND (((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms] OR Coronary Disease[MeSH Terms] OR Coronary Artery Disease[MeSH Terms] OR Heart Diseases[MeSH Terms] OR Cerebrovascular Diseases[MeSH Terms] OR Stroke[MeSH Terms]))))) AND ((India[MeSH Terms] OR Republic of India[MeSH Terms]))) – 31 results (Filters: Years between 2010 and 2020 and English language publication)

Google scholar: 635 + 22 + 6 + 12 = 675

ScienceDirect: (Diabetes Mellitus OR Cardiovascular Diseases OR Hypertension) AND (Qualitative Study OR Qualitative) AND (India) AND (Adherence) – 238 articles

Cochrane library: (Diabetes Mellitus OR Cardiovascular Diseases OR Hypertension) AND (Qualitative Study OR Qualitative) AND (India) AND (Adherence) – 34 articles

S1 Table. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ Checklist (Tong, *et al.*, 2012)

Item No.	Guide and Description	Report Location
1. Aim	State the research question the synthesis addresses	P 6, 1-13
2. Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology (e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis)	P9, 16-25 P10, 1-22
3. Approach to searching	Indicate whether the search was pre-planned (comprehensive search strategies to seek all available studies) or iterative (to seek all available concepts until they theoretical saturation is achieved)	P8, 1-10
4. Inclusion criteria	Specify the inclusion/exclusion criteria (e.g. in terms of population, language, year limits, type of publication, study type)	P7, 3-23
5. Data sources	Describe the information sources used (e.g. electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists) and when the searches conducted; provide the rationale for using the data sources	P8, 1-10
6. Electronic Search strategy	Describe the literature search (e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits)	Supplementary file 1
7. Study screening methods	Describe the process of study screening and sifting (e.g. title, abstract and full text review, number of independent reviewers who screened studies)	Figure 1
8. Study characteristics	Present the characteristics of the included studies (e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions)	Table 1
9. Study selection results	Identify the number of studies screened and provide reasons for study exclusion (e.g. for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications to the research question and/or contribution to theory development)	Fig 1 - PRISMA flow diagram P11, 6-18
10. Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings (e.g. assessment of conduct (validity and robustness),	P11, 14-18 Table 1

	assessment of reporting (transparency), assessment of content and utility of the findings)	
11. Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings (e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope [25]; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and interpretations, reporting)	P9, 3-14 Table 1
12. Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required	P8, 11-17
13. Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale	P11, 14-18 Table 1
14. Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? (e.g. all text under the headings "results /conclusions" were extracted electronically and entered into a computer software)	P8, 18-25
15. Software	State the computer software used, if any	None used
16. Number of reviewers	Identify who was involved in coding and analysis	P9, 16-22
17. Coding	Describe the process for coding of data (e.g. line by line coding to search for concepts)	P9, 23-35 P10, 1-22
18. Study comparison	Describe how were comparisons made within and across studies (e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary)	Table 2
19. Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive	Inductive process Table 2
20. Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation	Table 2
21. Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct)	P11-14

BMJ Open

Patient and Provider's perspective on barriers and facilitators for medication adherence among adult patients with Cardiovascular Diseases and Diabetes Mellitus in India – A qualitative evidence synthesis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055226.R2
Article Type:	Original research
Date Submitted by the Author:	15-Dec-2021
Complete List of Authors:	Krishnamoorthy, Yuvaraj; JIPMER PSM, Rajaa, Sathish; Jawaharlal Institute of Postgraduate Medical Education, Rehman, Tanveer; PGIMER Thulasingam, Mahalakshmi ; JIPMER, Department of Preventive and Social Medicine
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Cardiovascular medicine, Diabetes and endocrinology
Keywords:	QUALITATIVE RESEARCH, PREVENTIVE MEDICINE, PRIMARY CARE, Coronary heart disease < CARDIOLOGY, DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Patient and Provider's perspective on barriers and facilitators for medication adherence among adult patients with Cardiovascular Diseases and Diabetes Mellitus in India – A qualitative evidence synthesis

Running head: Barriers and facilitators for medication adherence among CVD and DM patients in India

Article category: Systematic Review

Yuvaraj Krishnamoorthy[1], Sathish Rajaa[2], Tanveer Rehman[3], Mahalakshmi Thulasingam[4]

[1]Assistant Professor, Department of Community Medicine, ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India;

Contact Number: +91 9551892665

Email id: yuvi.1130@gmail.com

[2]Assistant Professor, Department of Community Medicine, ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India;

Contact Number: +91 9791974633

Email id: psrajaa2410@gmail.com

[3]Independent Author, Kolkata, West Bengal, India

Contact Number: +91 8336922482

Email id: drtanveerrehman@gmail.com

[4]Associate Professor, Department of Preventive and Social Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry - 605006, India;

Contact Number: +91 9488729774

Email id: mahalakshmi.dr@gmail.com

Corresponding Author:

Dr Sathish Rajaa,

Assistant Professor,

Department of Community Medicine,

ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India

Contact Number: +91 9791974633

Email id: psrajaa2410@gmail.com

Abstract:

Objective:

To explore the various stakeholders' perspectives on barriers and facilitators for medication adherence among CVD and DM patients in India.

Methods:

A comprehensive systematic search was conducted in Medline, Cochrane library, Science Direct and Google Scholar from January 2010 to July 2020. We used the framework of the systems approach for healthcare delivery to conduct thematic analysis, using published qualitative literature to derive relevant themes, sub-themes and codes.

Setting: A Qualitative Evidence Synthesis of qualitative published studies from India

Subjects: A Qualitative Evidence Synthesis of the available qualitative evidence on the barriers and facilitating factors for medication adherence among CVD and DM patients in India

Results:

In total, 18 studies were included. Major barriers reported were lack of understanding about the disease, complications related to non-adherence, followed by forgetfulness, lack of family support and risk communication. Health system-related barriers such as accessibility, affordability, and acceptability were also reported by majority of the studies. Creation of peer support group, digital reminder system, integration of AYUSH, mental health, physiotherapy and geriatric clinics at primary healthcare level and innovations in patient care were suggested to counter these barriers in medication adherence.

Conclusion:

Such patient-specific targeted interventions need to be developed to achieve better control among CVD and DM patients.

Keywords: Cardiovascular Diseases, Diabetes Mellitus, Medication Adherence, Qualitative Research

Strengths and Limitations:

1. This is the first review exploring factors associated with drug adherence among CVD & DM patients in India
2. We have adhered to the ENTREQ statement ensuring transparency and reproducibility of the study findings.
3. We cannot rule out of the dissemination bias with respect to accurate and complete representation of the phenomenon of interest.
4. We focussed primarily on the patient and provider perspective on medication adherence. Hence, we cannot comment on the organizational or political influences on the adherence to long-term therapies.
5. The sample size of the included studies can be considered relatively low (median sample size - 30).

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality globally and in India.[1,2] More than a quarter (28%) of all deaths in India are attributable to CVDs with Ischemic heart disease (IHD) and stroke constituting the majority (83%).[3] On the other hand, India ranks second after China in the global diabetes epidemic, with a prevalence of around 10%.[4] Both diabetes mellitus (DM) and hypertension have long been recognized as independent risk factors for CVDs, whereas adherence to prescribed hypoglycaemic and antihypertensive drug therapies have significantly reduced the risk.[5-8] At least half of hypertensive & DM patients stop taking their medication within a year, often without informing their provider. With further nonadherence and attrition over time, medication adherence has emerged as a significant public health priority.[9]

Medication adherence is defined as the extent to which a person's behaviour coincides with the agreed medication regimen or health advice from a health care provider.[10] It has three components: initiation (when the patient takes the first dose of prescribed medication), implementation (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen), and discontinuation (when no more doses are taken after that).[11] Medication adherence is of growing interest to clinicians, healthcare systems, and other stakeholders (e.g., payers). There is soaring evidence that establishes nonadherence is often associated with lower quality of life, adverse clinical events, increased need for medical interventions, mortality, and thus giving rise to avoidable out-of-pocket expenditure in health.[12] Non-adherent hypertensive and stable coronary heart disease (CHD) patients have a four to five times higher risk of developing CHD and death, when compared to adherent patients.[13,14] Similarly, the likelihood of hospitalization is doubled among DM & hypertensive patients who are non-adherent to prescribed therapies compared to the general population. Despite recent advancements in pharmacologic treatment and technology to treat and monitor DM and CVD patients,

medication adherence is of particular concern in low-and-middle-income countries (LMIC) like India, where accessibility and affordability are still issues.[3,15]

Barriers to adherence can be comprehended as the patient, medication, provider, and health system factors, with interactions among them.[16,17] Patient factors that influence adherence include poor health literacy, cultural beliefs regarding medication effectiveness, and religious healing practices.[17] Low income, forgetting to take medication, and perceptions regarding pills like safety concerns, convenience, and necessity add to the above list.[16,17] Inadequate knowledge about a drug and its use, not being convinced of the need for medication, fear of adverse effects, and long-term treatment regimens also prompt medication discontinuation.[15] Clinician factors cover failure to recognize nonadherence, prescription of complex and multidrug regimens, ineffective communication of benefits of medications, and excluding patients in the treatment decision–making process.[17] Health system factors comprise limited insurance coverage, poor coordination of care between inpatient and outpatient settings, and inadequate communication between prescribers (i.e., specialists and primary care clinicians). In addition, the caregivers' aspect also becomes relevant in determining patients' adherence as CVD patients with a caregiver are more likely to be adherent to medications.[18] Hence identifying specific barriers for each patient and adopting suitable techniques to overcome them is imperative to improve medication adherence. Some of the facilitators successful in overcoming these barriers include a personal medication counsellor in the care continuum to guide patients with medication use, single-pill fixed-dose combinations, training pharmacists as coaches for drug therapies, building peer groups for chronic conditions, and developing information systems in the follow-up of patients.[19]

Quantitative studies have focused on medication adherence incidence and identification of its potential risk factors. They do not, however, uncover life circumstances that may influence adherence from the patient perspective. The inclusion of qualitative studies in our review will

provide a better understanding of the barriers and facilitators from the perspective and experiences of patients, healthcare providers, and caregivers.[20] Qualitative evidence synthesis, a novel research method, brings together the available qualitative evidence from primary studies through a systematic review process. Despite the evidence obtained from primary qualitative studies could be conceptually richer, a qualitative evidence synthesis can aid us in getting an overall view of the findings, and help us in addressing subtle and sensitive issues that most primary studies encounter. The findings from a qualitative evidence synthesis can guide us in crucial making policy recommendations in health care, retaining the impact of individual studies and group experiences. [21] Therefore, the current review was done to understand the perspective of various stakeholders (patients, caregivers, and healthcare providers) on the barriers and facilitators for medication adherence among CVD and DM patients in India. We also explored the suggestions and solutions provided by these stakeholders in overcoming the reported barriers.

METHODS

This review was performed by adhering to the "enhancing transparency in reporting the synthesis of qualitative research (ENTREQ)" statement. (Supplementary file 2) [22] We registered our protocol in the PROSPERO database (Registration number - CRD42020199529). We also searched PROSPERO and Cochrane to ensure that no similar review protocol has been reported. We also performed a preliminary search to ensure that no previous reviews of our similar topic targeting the Indian population were published.

Study design

We performed an evidence synthesis of the available qualitative evidence on the barriers and facilitating factors for medication adherence among CVD and DM patients. This review would

help to aggregate the evidence of peer-reviewed articles in this field and build an organized empirical research outline based on prior knowledge.

Eligibility criteria

Study type

We have included qualitative peer-reviewed studies conducted in India for our current review. Furthermore, qualitative evidence from other mixed methods studies was screened for eligibility and included in the qualitative component was relevant to our review. In addition, we included studies using qualitative techniques for data collection such as focussed group discussion (FGD), in-depth interviews (IDI), and Key Informant Interviews (KII).

Participant type

We have included the studies reporting the barriers and facilitators of medication adherence from patients' perspectives (CVD and DM), family members, healthcare workers (HCWs), or health system policymakers in India. HCWs were defined as per WHO recommendation as "all the persons involved in the actions whose primary intent is to enhance the health."[23]

Outcome

The phenomenon of interest in our review was to explore the barriers and facilitators for medication adherence among CVD and DM patients in India. We also explored the possible suggestions and solutions to address the barriers and improve compliance, as experienced by the patients, caregivers, family members, HCWs, and other relevant stakeholders.

Exclusion criteria

We have excluded the studies not available in English, books or conference abstracts or grey literature, or editorial comments. We have also excluded the studies reporting only quantitative data such as cross-sectional surveys, case-control, cohort studies, or intervention trials.

Search strategy

We have conducted a comprehensive and systematic search in databases and search engines such as Medline, Cochrane library, ScienceDirect, and Google Scholar. A combination of medical subject heading (MeSH) and free-full text terms was used for carrying out a literature search. The detailed search strategy and search results in the databases mentioned above and search engines are provided in Supplementary File 1. In addition to this, we also checked the reference list of primary studies obtained via electronic search and included articles relevant to our review and analysis. The search was conducted in all the databases from January 2010 to July 2020 with English language restriction for publication. Furthermore, the search timeline was restricted to ensure that our work provides a broader view and identifies the emerging issues.

Study selection process

Two investigators (YK and TR) independently performed the literature search, screened the title and abstract of all the identified studies, and retrieved the full text for articles relevant to our review. Further full-text screening of the retrieved articles was done again independently by the two investigators (YK, TR) to select the studies matching the eligibility criteria of our review. Disagreements during this process between the two investigators were resolved through consultation with a third investigator (SR).

Data Extraction and Management

After the study selection, two investigators (YK and TR) independently extracted the relevant data and study characteristics onto a predetermined data extraction format. Data entry was double-checked for accuracy by a third investigator (SR) by comparing the data presented in the review and individual study reports. As a result, we have extracted the following study characteristics: general information such as the name of the first author, the country in which the study was done, and year of publication, in the methods section, data collection period, study design, study participants, sample size, sampling technique, and data collection

procedure. In addition, barriers, facilitators, suggestions, and solutions to medication adherence were identified systematically.

Quality assessment

Two investigators (YK and SR) independently performed the quality check using the Critical Appraisal Skills Programme (CASP) criteria.[24] This checklist has been widely used for assessing the quality of studies included in this Qualitative Evidence synthesis.[25] This has helped determine whether the studies included are coherent with the quality appraisal standard for qualitative studies. This checklist consists of 10 questions concerning the study's clarity, methodology, and results to rank the included studies. Subsequently, these studies were stratified into high quality (three stars for studies scoring 8 to 10 points), medium quality (two stars for studies scoring 4 to 7 points), and low rate (one star for studies scoring 0 to 3 points). We did not exclude the low-quality studies, but the interpretation of results was made with caution. Disagreements during the quality assessment process were resolved by discussion with the third investigator (TR).

Data Analysis

We analysed and reported the findings in separate clusters such as patients, caregivers, family members, HCWs, and policymakers to demonstrate the differences among these subgroups. We have adopted a thematic framework analysis to analyse and synthesize the data. Thematic framework analysis has been helpful as the evidence was primarily descriptive and improved our understanding of the barriers and facilitators in medication adherence among CVD and DM patients. This framework synthesis has five stages of synthesizing the qualitative data.

First stage - Familiarisation with the data: Primary investigator (YK) did the process of familiarisation with data by reviewing all the selected articles against the objective of our review and found the recurrent themes across the included studies.

The second stage - Identifying the thematic framework: The investigators used a predetermined thematic framework developed using literature to guide the thematic analysis. The final framework comprised of a detailed list of facilitators and barriers for medication adherence and also solutions to address the issue.

Third stage - Indexing: Two independent investigators (YK and SR) read the extracted information and searched for themes as per the predetermined thematic framework and found additional emerging themes. The framework underwent several revisions as and when a new theme emerged. This has been performed through discussion and agreement between the entire team of investigators. Next, all the studies were completely read and examined till there was no new emergent theme. Coding of the data was then done as per the themes identified in our analysis. Finally, each preliminary study indexing was done using the codes related to the thematic framework. Whenever appropriate, sections of the studies were indexed with one or more codes.

Fourth stage - Charting: The investigators have sorted the data based on the themes and presented these themes in the tabular format (chart). The rows and columns of the table indicate the themes related to the studies, which enabled us to compare the study findings across various themes and subthemes.

***Fifth stage - Mapping and interpretation*:** The investigators used these charts to define the concepts identified, and mapped the nature and range of the phenomena. Our review explored the associations between the various themes and helped in clarifying the findings. Finally, we mapped and interpreted the findings in line with our objectives and emergent themes.

Ethical considerations

Approval from an ethics committee is not required since our review included only publicly available data without involving the human participants directly.

Patient and Public Involvement:

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Study selection

A comprehensive and systematic search was done to identify the relevant studies from January 2010 to July 2020. In total, we identified 1187 citations, and after the removal of duplicates from multiple databases, 982 records were screened for their title and abstract and assessed for eligibility. From these records, we retrieved 33 articles, and after going through the full text of these articles, 18 studies were included in the review. (**Figure 1**).[26-43]

Characteristics of the studies included

Characteristics of the included studies are reported in **Table 1**. Of the 18 studies included, 9 (50%) were from the Southern region, followed by 7 (38%) from the Northern part of India. The mean age of the participants ranged from 25-76 years. The typology of the studies comprised of in-depth interviews (IDIs) and focussed group discussions (FGDs). The study participants were primarily patients with diabetes, hypertension, or any cardiovascular diseases (to explore the patient perspective), and health care workers (4 studies) providing care to them (to obtain the provider perspective). The total sample size of the included studies ranged from 6 to 100. The majority (10 of the included studies) were done in a community setting, while the rest were either facility-based or had participants from ongoing trials. Four of the included studies used software for analysing the qualitative data, while the rest followed manual methods. Most of the included studies (14 out of 18) had higher ratings indicating high-quality evidence.

Narrative synthesis

Significant findings from the review showed that factors contributory to adherence come under three themes: patient-related, family-related, and health system-related factors. The barriers, facilitators, and suggestions to improve medication adherence were summarized under these three themes.

Barriers in medication adherence

Table-2 shows the thematic framework analysis related to barriers in medication adherence among CVD and DM patients. All the 18 included studies have explored and reported on these barriers.

Patient-related factors

Significant patient-related barriers (10 studies) reported were lack of knowledge or understanding about the disease, its complications related to nonadherence, and the treatment schedule, followed by forgetfulness to take medicine (7 studies). Reasons provided for the same were the patients' busy schedule, laziness, or forgetting to take the medication while traveling out-of-station. Patients have also reported certain misconceptions about the medicines like the risk of long-term neurological illness because of medication intake, inferior quality of drugs provided in hospitals, and wrong perception about stopping the medications once the patient feels normal. Patients in some studies have reported that they practice alternate systems of medicine such as herbal medicines and avoid taking allopathic medicines leading to poorer control of their condition. Substance use such as alcohol or tobacco use, side effects related to drugs, stress, and stigma were reported to be other barriers

Family-related factors

The patients and providers have reported a lack of family support as a significant contributing factor for nonadherence. In addition, the lack of social and emotional support to the patients further contributes to the nonadherence among the patients suffering from CVDs and DM.

Domestic works, personal priorities, commitments, or other issues hinder the family members from providing the above-mentioned support to the patients.

Health system-related factors

In most of these studies, providers were also interviewed to understand the factors related to the health system responsible for nonadherence among CVD and DM patients. Healthcare providers and patients interviewed, in almost all these studies, have reported affordability, accessibility, and acceptability as the major factors hindering medication adherence. Affordability is an issue with patients seeking healthcare in private facilities and patients getting care in public healthcare facilities. Though there was no direct medical cost related to government hospitals or primary healthcare centres, direct non-medical costs such as transport (due to poor accessibility) and indirect costs such as loss of wages (due to inconvenient consultation timing) were higher amongst these patients. In addition, patients have a wrong perception that medications in public facilities are of poorer quality, making them choose private health facilities, including those belonging to lower socioeconomic status. Lack of risk communication, counselling, or empathy by the physicians mainly due to overburdening public health facilities and time constraints were the other health system-related barriers reported by the providers and patients.

Facilitators in medication adherence

Facilitators in medication adherence were also summarized using the pre-existing thematic framework (**Table-3**). In total, ten studies have explored the facilitators in medication adherence from the patient or providers' perspective.

Patient-related factors

Most of the studies (5 studies) reported fear of complications due to nonadherence and self-perception of being healthy (once they adhere to the medications) as the significant facilitators. In addition, having a reminder system in the form of a reminder notebook, separate

pillboxes/cases/covers, or personalized shelf facilitates the patients in adhering to the medications. Some studies have also reported that integrating drug intake into daily routine activities and peer influence acts as a good facilitator in compliance with medications.

Family-related factors

Family support was reported as a major facilitating factor for compliance with medication. Apart from the support, adverse experiences in the past, such as death or severe complications among the family members, instilled fear in the patients, making them more compliant to the medications.

Health system-related factors

Barriers reported in some of the studies, such as empathy and counselling by healthcare providers, were considered facilitators by the other studies' patients. Another major facilitator from the health system side is the trust that patient has in their physician and their willingness to effectively follow advice related to self-care and adherence. Other familiar facilitators reported by the patients and providers were the use of dedicated pill cover/boxes for each drug provided in the clinic, linkage of health services with NGO for provision of counselling and generating awareness, availability of medication, and use of polypills.

Suggestions to improve medication adherence

Suggestions and solutions to enhance the compliance to medication were reported in 16 out of the 18 included studies based on either patient or provider's perspective (**Table-4**). Few suggestions were related to patients and family members, while the majority were related to the change in the health system.

Patient and family-related factors

Creating or joining a peer support group was one of the major suggestions related to the patients. This will help by motivating the patients to be more compliant with medications and

other self-care practices. Digital reminder systems using a watch and a mobile phone can also improve medication adherence.

Health system-related factors

Innovations in patient care, have been necessitated as an important factor to promote drug adherence. Some of the innovations suggested were dedicated days for specific disease conditions to avoid overburdening the facilities, a dedicated counselling station for drug adherence during the clinic with separate human resources, and a unique pill dispensing mechanism like colour coding, etc. In addition, Information Education and Communication (IEC)/Behaviour change communication (BCC) campaigns, digitalizing the patient treatment records, linkage of healthcare services with NGOs or community-based organizations, regular training of healthcare workers, and promotion of polypill use were other common suggestions offered by the healthcare providers.

Discussion

We conducted this review to integrate the qualitative evidence on barriers and facilitators for medication adherence among CVD and DM patients in India. We also further explored the suggestions to improve the same. The studies included in our review involved a total of 636 participants (534 CVD and DM patients, 102 healthcare providers). The majority of the included studies were of high quality concerning study clarity, methodology, and results. We summarized under three major themes: barriers, facilitators, suggestions and reported the findings under the following four sub-themes: patients, care team, healthcare organization, and environment-related factors.

Comparison of findings with previous literature

Barriers in medication adherence

Major barriers were lack of patient's understanding about the disease and its complications, forgetfulness, and misconception about the medications. Lack of family support was seen as a

major barrier from both patient's and provider's perspectives. In addition to these factors, stress and stigma were also mentioned as important factors among patients to not take medicine on time. In addition to the above, medication adherence could also be highly hindered by the patients' cultural beliefs, perceived discrimination, and social customs, which are highly prevalent in a culturally influenced country like India. A few studies have also shown evidence of improvement in medication adherence where efforts were taken to overcome the cultural barriers. [44] We also found major health system-related barriers were lack of accessibility and availability, higher cost of medications, and poor physician attitude. These findings were in line with the previous review conducted among South-East Asian DM patients.[44,46] In addition, our findings of patients related factors were found to be similar to other patients belonging to non-English speaking Hispanic, South American ethnic groups, as they also had misconceptions related to therapy, lack of understanding about their condition, with additional stress and stigma as a factor for non-adherence.[47-49]

Facilitators in medication adherence

Fear of complications, self-perception of being healthy, having a reminder system was reported as major facilitators by patients. Physician trust, advice, empathy, and counselling were the other provider-related facilitators in adhering to medications. Common facilitators as reported by the patients and providers were: dedicated pill cover/boxes for each drug provided in the clinic, availability of medication, and use of polypills. These findings were also in line with the previous qualitative reviews conducted in low middle-income countries including India.[47-50]

Suggestions to improve medication adherence

The solutions provided by the patients and health professionals were in line with the barriers identified in our review. Proper physician counselling to make the patients understand their own condition, complications of the disease and avoid misconception about the drugs and their side effects, good family support, making the medication accessible and available free of cost

were suggested as major suggestions to improve medication adherence. Similar interventions were also suggested by previous qualitative evidence on medication adherence among CVD and DM patients.[45-49] It is also interesting to note that medication adherence is also hurdled by the patients' intention towards adherence, and this intention might vary across nations and cultural groups. The patient's intention not to refill prescriptions due to cost, not to take medication because the patient feels better, also influences the patient's decision. Thus future research exploring these reasons on patient's choice to adhere or not, rather than an inability to adhere (e.g., forgetting, no access) needs to be encouraged.

Strengths and limitations of the study

To the best of our knowledge, this is the first review exploring and synthesizing the qualitative factors associated with medication adherence among CVD and DM patients in India. We have provided comprehensive and systematic evidence on the barriers, facilitators related to medication adherence, adhering to the ENTREQ statement, and ensuring transparency and reproducibility. We examined this evidence through the lenses of a well-established theoretical framework model. Moreover, our study was able to provide valuable suggestions to promote medication adherence from both patient's and provider's perspectives. In addition to these strengths, we found that the highest-rated studies contributed to the majority of the factors found in our review. This in turn ensures the transferability (external validity) of our review findings.

However, our review has certain limitations. We did not search grey literature, possibly missing some insights for our review. Hence, we cannot rule out the dissemination bias for an accurate and complete representation of the phenomenon of interest. We focussed primarily on the patient and provider perspective on medication adherence.[51] Hence, we cannot comment on the organizational or political influences on the adherence to long-term therapies as mentioned in the WHO report.[16] The sample size of the included studies can be considered relatively low

(median sample size - 30). However, all the studies were conducted till the achievement of data saturation. In addition to the above, these results and suggestions need to be considered after taking into account India's cross-cultural adaptations, customs, linguistic variations, and genetic susceptibility, and higher prevalence of risk factor profile.

Implications for clinical and public health practice

Improving medication adherence is essential to achieve better control and prevent life-threatening complications. Factors related to patients such as self-awareness and fear about the condition and its complications acted as a major facilitator for medication adherence. We also found more modifiable barriers related to medication intakes such as forgetfulness, lack of knowledge, and misconception about medications. Interventions should focus on these modifiable barriers such as knowledge barriers, intention barriers, and health system-related barriers to achieve better adherence. In addition, the family members need to help the patients in mapping their daily routine and link the medicine intake with these routines to facilitate adherence. Our review also suggested that healthcare providers play an important role in promoting medication adherence. Hence, the interventions should not only target the patients but also the family members and healthcare providers and they should be tailored to suit differences in setting, culture, and type of the patients.

Implications for future research

More evidence needs to be generated concerning the solutions obtained in our review such as memory tools including the digital solutions, polypills, peer support groups, etc. Further qualitative studies including the subgroup of patients with CVD and DM under different stages and treatment regimens are required to contextualize the medication adherence. Exploring the barriers using a theoretical framework with the same methodological approach, can provide more reliable evidence to develop patient-centered interventions and achieve better control among CVD and DM patients.

Conclusion:

In our review, we categorised the facilitating factors and barriers influencing medication adherence into patient-related, health system-related, and care team-related factors. Thus, we advocate the creation of peer support groups, the use of a digital reminder system for overcoming patients related factors, and integration of AYUSH services, mental health, physiotherapy, and geriatric clinics even at the primary healthcare level for overcoming the health system-related barriers towards medication adherence.

Funding: None

Competing interests statement: None declared

Acknowledgements: None

Author contribution statement: Conceived and designed the study: YK & SR, Data management and extraction: YK, SR & TR, Analysed the data and wrote the paper: SR, YK & TR. Provided comments and inputs to revise the manuscript: SR, YK, TR & MT

Data sharing statement: The authors confirm that the data supporting the findings of this study are available within the article

References:

1. Walker IF, Garbe F, Wright J, Newell I, Athiraman N, Khan N, et al. The Economic Costs of Cardiovascular Disease, Diabetes Mellitus, and Associated Complications in South Asia: A Systematic Review. Value Health Reg Issues. 2018;15:12–26.
2. Glovaci D, Fan W, Wong ND. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. Curr Cardiol Rep. 2019;21:21.
3. Prabhakaran D, Jeemon P, Sharma M, Roth GA, Johnson C, Harikrishnan S, et al. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018;6:e1339–51.

4. Tandon N, Anjana RM, Mohan V, Kaur T, Afshin A, Ong K, et al. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018;6:e1352–62.
5. Durand H, Hayes P, Morrissey EC, Newell J, Casey M, Murphy AW, et al. Medication adherence among patients with apparent treatment-resistant hypertension: systematic review and meta-analysis. J Hypertens. 2017;35:2346–57.
6. Polypharmacy and Medication Adherence in Patients With Type 2 Diabetes | Diabetes Care [Internet]. [cited 2020 Jul 30]. Available from: https://care.diabetesjournals.org/content/26/5/1408.short
7. Vrijens B, Antoniou S, Burnier M, de la Sierra A, Volpe M. Current Situation of Medication Adherence in Hypertension. Front Pharmacol [Internet]. 2017 [cited 2020 Jul 31];8. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2017.00100/full
8. Rehman T, Rajaa S, Kumar G, Jayalakshmy R. Prevalence and factors influencing diabesity among persons with type 2 diabetes mellitus in urban Puducherry: A cross-sectional analytical study. Indian J Community Med. 2020 Jul;45(3):315.
9. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence. 2016;10:1299–307.
10. Leporini C, De Sarro G, Russo E. Adherence to therapy and adverse drug reactions: is there a link? Expert Opin Drug Saf. 2014;13 Suppl 1:S41-55.
11. Lam WY, Fresco P. Medication Adherence Measures: An Overview. BioMed Res Int. 2015; 2015:1–12.
12. Kvarnström K, Airaksinen M, Liira H. Barriers and facilitators to medication adherence: a qualitative study with general practitioners. BMJ Open. 2018;8:e015332.

13. Ferdinand KC, Senatore FF, Clayton-Jeter H, Cryer DR, Lewin JC, Nasser SA, et al. Improving Medication Adherence in Cardiometabolic Disease. J Am Coll Cardiol. 2017;69:437–51.

14. Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. Adv Ther. 2005;22:313–56.

15. Dennis T, Meera NK, Binny K, Sekhar MS, Kishore G, Sasidharan S. Medication adherence and associated barriers in hypertension management in India. CVD Prev Control. 2011 Jan 1;6(1):9-13.

16. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. Circulation. 1997;95:1085–90.

17. WHO | ADHERENCE TO LONG-TERM THERAPIES: EVIDENCE FOR ACTION [Internet]. WHO. World Health Organization; [cited 2020 Jul 30]. Available from: http://www.who.int/chp/knowledge/publications/adherence_report/en/

18. Aggarwal B, Liao M, Mosca L. Medication Adherence Is Associated with Having a Caregiver Among Cardiac Patients. Ann Behav Med Publ Soc Behav Med. 2013;46:237–42.

19. Daliri S, Bekker CL, Buurman BM, Scholte op Reimer WJM, van den Bemt BJF, Karapinar – Çarkit F. Barriers and facilitators with medication use during the transition from hospital to home: a qualitative study among patients. BMC Health Serv Res. 2019; 19:204.

20. Rathbone AP, Todd A, Jamie K, Bonam M, Banks L, Husband AK. A systematic review and thematic synthesis of patients' experience of medicines adherence. Res Social Admin Pharm. 2017 May 1;13(3):403-39.

21. Flemming K, Booth A, Garside R, Tunçalp Ö, Noyes J. Qualitative evidence synthesis for complex interventions and guideline development: clarification of the purpose, designs and relevant methods. BMJ Global Health. 2019 Jan 1;4(Suppl 1):e000882.

22. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012; 12:181

23. Mohanty A, Kabi A, Mohanty AP. Health problems in healthcare workers: A review. J Family Med Primary Care. 2019 Aug;8(8):2568.

24. Critical Appraisal Skills Programme (2018). CASP (Qualitative) Checklist. [online] Available at: https://casp-uk.net/wp-content/uploads/2018/01/CASP-Qualitative-Checklist-2018.pdf Accessed: 12 September 2020

25. Booth A, Noyes J, Flemming K, Gerhardus A, Wahlster P, van der Wilt GJ,et al. Structured methodology review identified seven (RETREAT) criteria for selecting qualitative evidence synthesis approaches. J Clin Epidemiol. 2018 Jul 1;99:41-52.

26. Agarwal A, Davies D, Goenka S, Prabhakaran D, Huffman MD, Mohanan PP. Facilitators and barriers of heart failure care in Kerala, India: A qualitative analysis of healthcare providers and administrators. Indian Heart J. 2019; 71(3):235–41.

27. Dhar L. Perceptions of global coronary heart disease risk, and adherence to antihypertensive treatment among low income urban women in Delhi, India (Doctoral dissertation, Curtin University).

28. George CE, Ramadas D, Norman G, Mukherjee D, Rao T. Barriers to cardiovascular disease risk reduction: Does physicians' perspective matter? Indian Heart J. 2016; 68(3):278–85

29. Gupta S, Dhamija JP, Mohan I, Gupta R. Qualitative Study of Barriers to Adherence to Antihypertensive Medication among Rural Women in India. Int J Hypertens. 2019; 2019:1–7.

30. Gupta S, Virk A, Mittal A, Agarwal B. Patterns and determinants of healthcare-seeking behavior among hypertensive patients in a rural population of north India: A mixed-method study. J Family Med Prim Care. 2020; 9(6):2830

31. Jayanna K, Swaroop N, Kar A, Ramanaik S, Pati MK, Pujar A, et al. Designing a comprehensive Non-Communicable Diseases (NCD) programme for hypertension and diabetes at primary health care level: evidence and experience from urban Karnataka, South India. BMC Public Health. 2019; 19:1

32. Krishnamoorthy Y, Giriyappa DK, Eliyas SK, Priyan S, Saya GK, Lakshminarayanan S. Patient and Provider's Experience and Perspective in Addressing Barriers to Medication Adherence Among Noncommunicable Disease Patients in Rural Puducherry, South India—A Qualitative Study. J Patient Exp. 2019; 6(3):216–23

33. Kusuma YS. Migrants' Perceptions on Barriers to Treatment Seeking for Hypertension: A Qualitative Study from Delhi, India. Studies on Ethno-Medicine. 2010; 4(3):173–6

34. Miller V, Nambiar L, Saxena M, Leong D, Banerjee A et al. Exploring the barriers to and facilitators of using evidence-based drugs in the secondary prevention of cardiovascular diseases: findings from a multistakeholder, qualitative analysis. Global Heart. 2018; 13(1):27-34.

35. Newtonraj A, Arun S, Bazroy J, Tovia S. Lay perspectives on causes and complications of hypertension; and barrier to access health care by known hypertensive patients: a qualitative study from a rural area of South India. Int J Community Med Public Health. 2017; 4(3):704

36. Nimesh VV, Halder A, Mitra A, Kumar S, Joshi A, Joshi R, et al. Patterns of healthcare seeking behavior among persons with diabetes in Central India: A mixed method study. J Family Med Prim Care. 2019; 8(2):677.

37. Pati S, Van den Akker M, Schellevis FF, Sahoo K, Burgers JS. Managing diabetes mellitus with comorbidities in primary healthcare facilities: a qualitative study among physicians in Odisha, India. 2020. Research square [preprint] doi: 10.21203/rs.3.rs-22272/v1

38. Anitha Rani M, Shriraam V. Are Patients With Type 2 Diabetes Not Aware or Are They Unable to Practice Self-Care? A Qualitative Study in Rural South India. J Prim Care Community Health. 2019; 10:2150132719865820.

39. Salam A, Praveen D, Patel A, Tewari A, Webster R. Barriers and facilitators to the use of cardiovascular fixed-dose combination medication (polypills) in Andhra Pradesh, India: a mixed-methods study. Global Heart. 2019; 14(3):303-10.

40. Satish P, Khetan A, Barbhaya D, Agarwal M, Mohan SK, Josephson R, Webel AR. A qualitative study of facilitators and barriers to cardiovascular risk factor control in a semiurban population in India. J Family Med Prim Care. 2019; 8(12):3773-3778.

41. Thakur JS, Vijayvergiya R, Jaswal N, Ginsburg A. Assessment and barriers to medication adherence for secondary prevention of cardiovascular disease among patients with coronary artery disease in Chandigarh, India. Int J Non-Commun Dis. 2016;1:37-41.

42. Venkatesan M, Dongre AR, Ganapathy K. A community-based study on diabetes medication nonadherence and its risk factors in rural Tamil Nadu. Indian J Community Med. 2018; 43(2):72-76

43. Wood F, Salam A, Singh K, Day S, Jan S, Prabhakaran D, et al. Process evaluation of the impact and acceptability of a polypill for prevention of cardiovascular disease. BMJ Open. 2015; 5(9):e008018

44. Saha S, Korthuis PT, Cohn JA, Sharp VL, Moore RD, Beach MC. Primary care provider cultural competence and racial disparities in HIV care and outcomes. J Gen Intern Med. 2013;28(5):622-9. https://doi. org/10.1007/s11606-012-2298-8.

45. Sohal T, Sohal P, King-Shier KM, Khan NA. Barriers and Facilitators for Type-2 Diabetes Management in South Asians: A Systematic Review. PLoS ONE. 2015; 10(9): e0136202.

46. Sears K, Scobie A, MacKinnon NJ. Patient-related risk factors for self-reported medication errors in hospital and community settings in 8 countries. Can Pharm J: Revue des Pharmaciens du Canada. 2012 Mar;145(2):88-93.

47. Nam S, Chesla C, Stotts NA, Kroon L, Janson SL. Barriers to diabetes management: patient and provider factors. Diabetes Res Clin Pract. 2011; 93(1):1–9

48. Lipton RB, Losey LM, Giachello A, Mendez J, Girotti MH. Attitudes and issues in treating Latino patients with type 2 diabetes: views of healthcare providers. Diabetes Educ. 1998; 24: 67–71

49. Sridharan SG, Chittem M, Maya S. Patients' Experiences of Barriers and Facilitators for Adherence to Type 2 Diabetes Mellitus: A Meta-Ethnography. Journal of Social Health and Diabetes. 2019 Dec;7(02):61-72.

50. Al Hamid A, Ghaleb M, Aljadhey H, et al. A systematic review of qualitative research on the contributory factors leading to medicine-related problems from the perspectives of adult patients with cardiovascular diseases and diabetes mellitus. BMJ Open 2014; 4:e005992.

51. Toews I, Booth A, Berg RC et al. Further exploration of dissemination bias in qualitative research required to facilitate assessment within qualitative evidence synthesis. J Clin Epidemiol 2017; 88:133–139

Figure 1: Flow chart showing the search strategy and selection of studies

Table 1: Characteristics of the studies included (N=18)

S.No	Author and year	State	Data collection method	Study participants	Study setting	Approach	Coding	Theoretical framework used	Method of analysis	Sample size	Mean Age in years	Study quality
1.	Agarwal 2019	Kerala	IDI	Clinical and administrative staff	Facility based	NR	Inductive	NR	Dedoose Software	21	NR	***
2.	Dhar et al 2016	Delhi	IDI	Hypertensive women aged 35-59 years	Community based	NR	Inductive	Yes	Manual content analysis	30	48	***
3.	George et al 2016	Karnataka	IDI	Physicians providing Non communicable disease care	Community based	NR	Inductive	NR	Manual content analysis	36	46	***
4.	Gupta et al 2019	Rajasthan	IDI	Hypertensive women	Facility based	NR	NR	NR	Manual content analysis	30	56	**
5.	Gupta et al 2020	Haryana	IDI	Hypertension patients	Facility based	NR	NR	NR	Manual content analysis	100	38-76	***
6.	Jayanna et al 2019	Karnataka	IDI & FGD	Diabetes and Hypertension patients	Facility based	NR	NR	Yes	Manual content analysis	10 IDI + 20 FGDs	NR	***
7.	Krishnamoorthy et al 2018	Puducherry	IDI & KII	Diabetes and Hypertension patients & Healthcare workers	Community based	NR	Inductive	NR	Manual content analysis	6 IDI + 4 KII	NR	***
8.	Kusuma et al 2010	Delhi	KII & FGD	Recent and Settled Migrants having hypertension inhabited in Delhi	Community based	NR	NR	NR	Manual content analysis	14 (KII) + 20 (FGD)	38 – 50 (KII) & 25 – 40 (FGD)	***
9.	Miller et al 2017	Delhi	IDI	Cardiovascular disease patients	Trial based	Descriptive	NR	NR	Manual content analysis	14	NR	***
10.	Newtonraj et al 2017	Tamil Nadu	Personal interviews	Hypertensive patients	Community based	NR	NR	NR	Manual content analysis	40	NR	**

11.	Nimesh et al 2019	Madhya Pradesh	IDI	Individuals with diabetes	Community based	NR	Inductive	Yes	Manual content analysis	60	52	***
12.	Patti et al 2020	Orissa	IDI	Primary care physicians	Facility based	NR	NR	NR	Manual content analysis	17	40	***
13.	Rani et al 2019	Tamil Nadu	FGD	Individuals with diabetes	Community based	Descriptive	NR	NR	Manual content analysis	50	50	**
14.	Salaam et al 2019	Andhra Pradesh	IDI	Patients with Cardiovascular disease	Community based	NR	NR	Yes	NVivo version 11 software	12	62	***
15.	Satish et al 2019	West Bengal	FGD	Patients with hypertension and/or diabetes	Trial based	NR	NR	Yes	Manual content analysis	70	53	***
16.	Thakur et al 2016	Chandigarh	IDI & FGD	Coronary artery disease patients	Facility based	NR	NR	NR	Manual Thematic analysis	20	NR	*
17.	Venkatesan et al 2018	Tamil Nadu	IDI	Health care workers	Community based	NR	NR	NR	Anthropac software	10	NR	***
18.	Wood et al 2015	Hyderabad and Delhi	IDI	Patients with Cardiovascular diseases	Trial based	NR	NR	Yes	NVivo software	52	57	***

NR – Not Reported
IDI – In depth Interview
FGD – Focussed Group Discussion
KII – Key informant interview

Table 2: Thematic framework analysis for summarizing barriers in medication adherence experienced by CVD & DM patients in India

Main theme/Sub-themes	Barriers in Medication Adherence	Studies
PATIENTS	1. **Lack of awareness/knowledge:** Lack of knowledge and understanding about the disease, its complications and treatment among the patients	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Newtonraj et al 2017, Patti et al 2020, Tan et al 2017, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	2. Forgetfulness: Patients forget to take medicine because of busy schedule	**Dhar et al 2016, Gupta et al 2019, Gupta et al 2020, Rani et al 2019, Venkatesan et al 2018, Wood et al 2015, Tan et al 2017, Thakur et al 2016**
	3. Misconception about medications: Patient has wrong perception about the medications, especially about its side effects and quality	**George et al 2016, Gupta et al 2020, Patti et al 2020, Rani et al 2019, Salaam et al 2019, Tan et al 2017, Venkatesan et al 2018**
	4. Preference to alternate system of medicine: Patients prefers taking herbal and other alternate system of medicines for their condition	**George et al 2016, Tan et al 2017, Venkatesan et al 2018**
	5. Ill effects of substance abuse: Patients have difficulty in adhering to medications during the bout of tobacco or alcohol consumption	**Jayanna et al 2019, Krishnamoorthy et al 2018**
	6. Effect of side effects: Patients stop their medication once they develop side effects related to the drugs	**Venkatesan et al 2018, Wood et al 2015**
	7. Stress: Patients developing stress due to personal or work-related problems are more non-adherent to medications	**Krishnamoorthy et al 2018**
	8. Stigma: Patients feel stigmatised in revealing their disease status to other family/friends leading to lack of support from them	**Krishnamoorthy et al 2018**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Family support:** Lack of physical, emotional and social support as the family members are pre-occupied with domestic works, crisis, other priorities and commitments	**Dhar et al 2016, George et al 2016, Gupta et al 2020, Krishnamoorthy et al 2018, Kusuma et al 2010, Newtonraj et al 2017, Rani et al 2019, Wood et al 2015**
	2. Risk communication: Poor risk communication or counselling to patients and family members about non-adherence to medication by the treating physicians	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Thakur et al 2016**
	3. Physician attitude: Lack of respect, empathy, communication and attention towards patients by the treating physicians	**Dhar et al 2016, Gupta et al 2019, Kusuma et al 2010, Jayanna et al 2019**

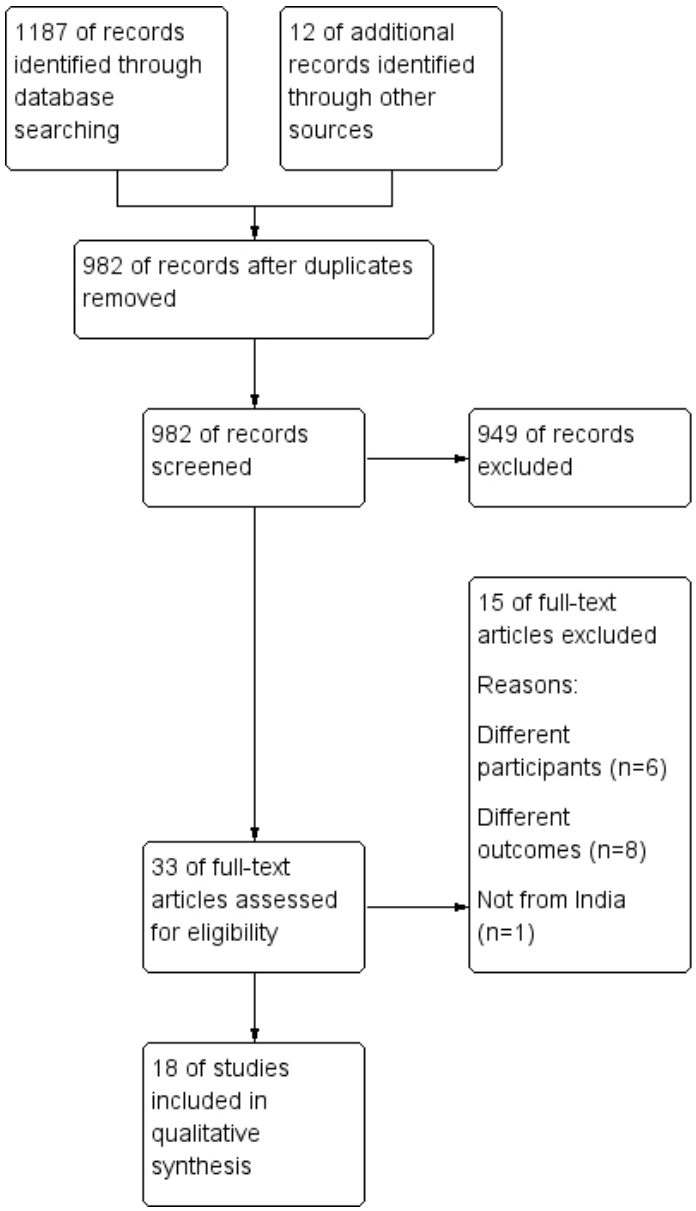
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Affordability:** Patients lose their daily wages due to inconvenient consultation timings in public facilities, which is aggravated by travel costs due to poor access, and higher medication costs while preferring private facilities	**Agarwal et al 2019, Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Kusuma et al 2010, Miller et al 2017, Nimesh et al 2019, Salaam et al 2019, Satish et al 2019, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	2. Accessibility: Lack of access to healthcare facilities (more distance) requiring longer travel and waiting time.	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Miller et al 2017, Newtonraj et al 2017, Tan et al 2017, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	3. Availability: Non-availability of essential medicines in public healthcare facilities	**Dhar et al 2016, Jayanna et al 2019, Kusuma et al 2010, Miller et al 2017, Newtonraj et al 2017, Patti et al 2020, Salaam et al 2019, Wood et al 2015**
	4. Acceptability: Medications from public health facilities are not acceptable to the patients due to poorer quality	
	5. Overburdening of primary health centres: Burdening of primary health facilities lead to time constraints in patient counselling regarding medication adherence	**Jayanna et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Patti et al 2020, Venkatesan et al 2018**

Table 3: Thematic framework for summarizing facilitators in medication adherence experienced by CVD & DM patients in India

Main theme/Sub-themes	Facilitators in Medication Adherence	Studies
PATIENTS	**1. Self-awareness and fear:** Patient's understanding about medicine adherence and fear about complications of non-adherence keeps them healthy	**Krishnamoorthy et al 2018, Miller et al 2017, Patti et al 2020, Satish et al 2019, Tan et al 2017, Wood et al 2015**
	2. Medicine Reminder system: Separate pill boxes/cases/covers, personalized shelf, and maintaining drug record notebook helps them in remembering daily doses	**Dhar et al 2016, Krishnamoorthy et al 2018, Miller et al 2017, Tan et al 2017**
	3. Integrating drug intake with the daily routine: Fixed time for medicine intake, separate place for keeping drug, and making arrangements during travel helps them in adherence	**Dhar et al 2016, Krishnamoorthy et al 2018**
	4. Positive peer influence: Good adherence to medication by the patient's peers motivates the patient to be compliance to their own drug intake	**Gupta et al 2019, Krishnamoorthy et al 2018**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Family support**: Constant reminders by family members for drug intake	**Dhar et al 2016, Gupta et al 2020, Krishnamoorthy et al 2018, Miller et al 2017, Wood et al 2015**
	2. Past adverse experiences: Death of patients' own family members due to complications of the condition has motivated them to adhere to medication	**Dhar et al 2016, Krishnamoorthy et al 2018**
	3. Healthcare provider counselling and empathy: Patients described that counselling from their healthcare providers has motivated them to remain adherent	**Kusuma et al 2010, Miller et al 2017, Patti et al 2020, Salaam et al 2019, Tan et al 2017**
	4. Trust in physician: Adherence is more when a positive rapport and trust is established between the patient and health care providers.	**Dhar et al 2016, Krishnamoorthy et al 2018, Satish et al 2019**
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Dedicated pill boxes/covers:** Provision of different medications in separate boxes/covers in the healthcare facility has helped as the patient to remember which medication to take at what time	**Krishnamoorthy et al 2018, Wood et al 2015**
	2. Combination drugs (polypills): Polypills had the following advantages to facilitate the medication adherence: a smaller number of pills, lower frequency, less chance of forgetting, potential for lower cost, and convenient simpler regimen	**Salaam et al 2019, Wood et al 2015**
	3. Availability of medications: Proper pharmacy inventory control and stock delivery has aided in medication adherence	**Miller et al 2017**
ENVIRONMENT (Regulatory, market and policy framework)	**1. NGO Support**: Patients has reported that sharing their concerns and receiving counselling from NGO/ Health officers acted as a facilitator for drug intake	**Tan et al 2017, Wood et al 2015**

Table 4: Thematic framework for summarizing suggestions to improve medication adherence among CVD & DM patients in India

Main theme/Sub-themes	Suggestions to improve medication adherence	Studies
PATIENTS	**1. Peer support groups:** Patients can motivate each other by forming support groups among themselves	**Krishnamoorthy et al 2018**
	2. Digital reminder system: Patient can use digital reminders such as watch, mobile phone to adhere to their drug schedule	**Krishnamoorthy et al 2018, Miller et al 2017**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Social support:** Family members can be educated and asked to provide support by reinforcing compliance, reminding about drug intake, motivating them patients to avoid substance abuse	**Agarwal et al 2019, Dhar et al 2016, Krishnamoorthy et al 2018, Nimesh et al 2019, Wood et al 2015**
	2. Financial support: Family members can provide financial support to cover the cost of medications, travel etc.	**Gupta et al 2019**
	3. Regular training of healthcare workers: Physicians and other healthcare workers involved in prescribing drugs and counselling should undergo regular training on standard treatment protocols	**George et al 2016, Jayanna et al 2019, Miller et al 2017, Patti et al 2020, Satish et al 2019**
	4. Team work approach: Integration of AYUSH, mental health counsellors, physiotherapist and geriatric clinics at primary healthcare level	**George et al 2016, Miller et al 2017, Patti et al 2020**
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Innovations in patient care:** Healthcare workers can make innovations like dedicated day for specific conditions (diabetes day, etc), dedicated counselling station/session with additional staff for detailing the importance of adherence and complications related to non-adherence, unique pill dispensing mechanism (colour coding)	**Agarwal et al 2019, Dhar et al 2016, Jayanna et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Newtonraj et al 2017, Patti et al 2020, Satish et al 2019, Venkatesan et al 2018, Wood et al 2015**
	2. IEC/BCC/Awareness campaigns: Putting up of IEC materials and conducting campaigns on importance of adherence in public places and workplaces	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Krishnamoorthy et al 2018, Newtonraj et al 2017, Patti et al 2020, Rani et al 2019**
	3. Digitalizing patient treatment record: Digitalizing a dedicated treatment record for each patient can help in better follow-up of the patient and improve adherence	**Jayanna et al 2019, Miller et al 2017, Patti et al 2020, Satish et al 2019, Wood et al 2015**
	4. Polypills: Disseminating the advantages of polypills to healthcare professionals by CME/conferences and patients by public education campaigns; Integration of polypills into clinical practice. etc	**Salaam et al 2019, Wood et al 2015**
ENVIRONMENT (Regulatory, market and policy framework)	**1. Linkage of health services with NGO and community-based organizations:** Community members, volunteers, anganwadi workers, self-help groups and NGO workers can be trained in counselling the patients to improve medication adherence	**Dhar et al 2016, Jayanna et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Miller et al 2017, Tan et al 2017**



141x246mm (72 x 72 DPI)

Supplementary Table 1 Search strategy

Key word	Alternative word
Qualitative studies	((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms] Case studies OR Focused group discussions OR phenomenological studies OR ethnographic studies OR interviews))
Medication Adherence	((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms])
Barriers, Facilitators and solutions	Challenges OR Challenge OR Problem OR Problems barriers OR Difficulties OR Issues OR Limitations OR Obstacles OR Facilitators OR Suggestions OR Solutions
Diabetes mellitus and CVDs	((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms] OR Coronary Disease[MeSH Terms] OR Coronary Artery Disease[MeSH Terms] OR Heart Diseases[MeSH Terms] OR Cerebrovascular Diseases[MeSH Terms] OR Stroke[MeSH Terms]))

India	(India[MeSH Terms] OR Republic of India[MeSH Terms]))

Search results (PubMed):

((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms])) AND ((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms]) OR Life Change Events[MeSH Terms]) OR Trust[MeSH Terms]))) AND ((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms])) AND (India[MeSH Terms] OR Republic of India[MeSH Terms])) – 199 (Filters: Years between 2010 and 2020 and English language publication)

((((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms] Case studies OR Focused group discussions OR phenomenological studies OR ethnographic studies OR interviews))) AND ((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms]))) AND (Challenges OR Challenge OR Problem OR Problems barriers OR Difficulties OR Issues OR Limitations OR Obstacles OR Facilitators OR Suggestions OR Solutions)) AND (((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms] OR Coronary Disease[MeSH Terms] OR Coronary Artery Disease[MeSH Terms] OR Heart Diseases[MeSH Terms] OR Cerebrovascular Diseases[MeSH Terms] OR Stroke[MeSH Terms]))))) AND ((India[MeSH Terms] OR Republic of India[MeSH Terms]))) – 31 results (Filters: Years between 2010 and 2020 and English language publication)

Google scholar: 635 + 22 + 6 + 12 = 675

ScienceDirect: (Diabetes Mellitus OR Cardiovascular Diseases OR Hypertension) AND (Qualitative Study OR Qualitative) AND (India) AND (Adherence) – 238 articles

Cochrane library: (Diabetes Mellitus OR Cardiovascular Diseases OR Hypertension) AND (Qualitative Study OR Qualitative) AND (India) AND (Adherence) – 34 articles

Supplementary file 2. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ Checklist (Tong, *et al.*, 2012)

Item No.	Guide and Description	Report Location
1. Aim	State the research question the synthesis addresses	P 6, 1-13
2. Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology (e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis)	P9, 16-25 P10, 1-22
3. Approach to searching	Indicate whether the search was pre-planned (comprehensive search strategies to seek all available studies) or iterative (to seek all available concepts until they theoretical saturation is achieved)	P8, 1-10
4. Inclusion criteria	Specify the inclusion/exclusion criteria (e.g. in terms of population, language, year limits, type of publication, study type)	P7, 3-23
5. Data sources	Describe the information sources used (e.g. electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists) and when the searches conducted; provide the rationale for using the data sources	P8, 1-10
6. Electronic Search strategy	Describe the literature search (e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits)	Supplementary file 1
7. Study screening methods	Describe the process of study screening and sifting (e.g. title, abstract and full text review, number of independent reviewers who screened studies)	Figure 1
8. Study characteristics	Present the characteristics of the included studies (e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions)	Table 1
9. Study selection results	Identify the number of studies screened and provide reasons for study exclusion (e.g. for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications to the research question and/or contribution to theory development)	Fig 1 - PRISMA flow diagram P11, 6-18
10. Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings (e.g. assessment of conduct (validity and robustness),	P11, 14-18 Table 1

	assessment of reporting (transparency), assessment of content and utility of the findings)	
11. Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings (e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope [25]; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and interpretations, reporting)	P9, 3-14 Table 1
12. Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required	P8, 11-17
13. Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale	P11, 14-18 Table 1
14. Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? (e.g. all text under the headings "results /conclusions" were extracted electronically and entered into a computer software)	P8, 18-25
15. Software	State the computer software used, if any	None used
16. Number of reviewers	Identify who was involved in coding and analysis	P9, 16-22
17. Coding	Describe the process for coding of data (e.g. line by line coding to search for concepts)	P9, 23-35 P10, 1-22
18. Study comparison	Describe how were comparisons made within and across studies (e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary)	Table 2
19. Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive	Inductive process Table 2
20. Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation	Table 2
21. Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct)	P11-14

BMJ Open

Patient and Provider's perspective on barriers and facilitators for medication adherence among adult patients with Cardiovascular Diseases and Diabetes Mellitus in India – A qualitative evidence synthesis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055226.R3
Article Type:	Original research
Date Submitted by the Author:	09-Feb-2022
Complete List of Authors:	Krishnamoorthy, Yuvaraj; JIPMER PSM, Rajaa, Sathish; Jawaharlal Institute of Postgraduate Medical Education, Rehman, Tanveer; PGIMER Thulasingam, Mahalakshmi ; JIPMER, Department of Preventive and Social Medicine
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Cardiovascular medicine, Diabetes and endocrinology
Keywords:	QUALITATIVE RESEARCH, PREVENTIVE MEDICINE, PRIMARY CARE, Coronary heart disease < CARDIOLOGY, DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Patient and provider's perspective on barriers and facilitators for medication adherence among adult patients with cardiovascular diseases and diabetes mellitus in India – A qualitative evidence synthesis

Running head: Barriers and facilitators for medication adherence among cardiovascular diseases and diabetes mellitus and DM patients in India

Article category: Systematic Review

Yuvaraj Krishnamoorthy[1], Sathish Rajaa[2], Tanveer Rehman[3], Mahalakshmi Thulasingam[4]

[1]Assistant Professor, Department of Community Medicine, ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India;

Contact Number: +91 9551892665

Email id: yuvi.1130@gmail.com

[2]Assistant Professor, Department of Community Medicine, ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India;

Contact Number: +91 9791974633

Email id: psrajaa2410@gmail.com

[3]Independent Author, Kolkata, West Bengal, India

Contact Number: +91 8336922482

Email id: drtanveerrehman@gmail.com

[4]Associate Professor, Department of Preventive and Social Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry - 605006, India;

Contact Number: +91 9488729774

Email id: mahalakshmi.dr@gmail.com

Corresponding Author:

Dr Sathish Rajaa,

Assistant Professor,

Department of Community Medicine,

ESIC Medical College & PGIMSR, K.K. Nagar, Chennai, India

Contact Number: +91 9791974633

Email id: psrajaa2410@gmail.com

Abstract:

Objective:

To explore the various stakeholders' perspectives on barriers and facilitators for medication adherence among cardiovascular diseases and diabetes mellitus patients in India.

Design: Systematic review of qualitative studies

Data sources:

A comprehensive systematic search was conducted in Medline, Cochrane Library, Science Direct and Google Scholar from January 2010 to July 2020. We included all qualitative peer-reviewed studies, reporting barriers and facilitators of medication adherence, from India for our current review.

Data extraction and synthesis: Data extraction was performed by two independent authors who also assessed the quality of included studies using the Critical Appraisal Skills Programme (CASP) criteria. This qualitative evidence synthesis adhered to the Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) checklist

Results:

In total, 18 studies were included. Major barriers reported were lack of understanding about the disease, complications related to non-adherence, followed by forgetfulness, lack of family support and risk communication. Health system-related barriers such as accessibility, affordability, and acceptability were also reported by majority of the studies. Creation of peer support groups, digital reminder systems, integration of native Indian systems of India,

physiotherapy and geriatric clinics at the primary healthcare level and innovations in patient care were suggested to counter these barriers in medication adherence.

Conclusion:

Such patient-specific targeted interventions need to be developed to achieve better control among CVD and DM patients.

Keywords: Cardiovascular Diseases, Diabetes Mellitus, Medication Adherence, Qualitative Research

Strengths and Limitations:

1. This is the first review exploring factors associated with drug adherence among cardiovascular diseases and diabetes mellitus patients in India
2. We have adhered to the ENTREQ statement ensuring transparency and reproducibility of the study findings.
3. We cannot rule out dissemination bias, causing selective reporting of studies with more non adherence to medications
4. We focussed primarily on the patient and provider perspective on medication adherence. Hence, we cannot comment on the organizational or political influences on the adherence to long-term therapies.
5. The sample size of the included studies can be considered relatively low (median sample size - 30).

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality globally and in India.[1,2] More than a quarter (28%) of all-cause mortality in India is attributed to CVDs, where ischemic heart disease (IHD) and stroke constitute the majority (83%).[3] On the other hand, India ranks second after China in the global diabetes epidemic, with a prevalence of around 10%.[4] Both diabetes mellitus (DM) and hypertension have long been recognized as independent risk factors for CVDs, whereas adherence to prescribed hypoglycaemic and antihypertensive drug therapies have significantly reduced the risk.[5-8] At least half of these chronic disease patients stop taking medications within a year, often without informing their provider. With further nonadherence and attrition over time, medication adherence has emerged as a significant public health priority.[9]

Medication adherence is defined as the extent to which a person's behaviour coincides with the agreed medication regimen or health advice from a health care provider.[10] It has three components: initiation (when the patient takes the first dose of prescribed medication), implementation (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen), and discontinuation (when no more doses are taken after that).[11] Medication adherence is of growing interest to clinicians, healthcare systems, and other stakeholders. There is soaring evidence that links nonadherence with lower quality of life, adverse clinical events, increased need for medical interventions, and mortality, thus giving rise to avoidable out-of-pocket expenditure in health.[12] Non-adherent hypertensive and stable coronary heart disease (CHD) patients have a four to five times higher risk of developing CHD and death, when compared to adherent patients.[13,14] Similarly, the likelihood of hospitalization is doubled among DM & hypertensive patients who are non-adherent to prescribed therapies compared to the general population. Despite recent advancements in pharmacologic treatment and technology to treat and monitor DM and CVD patients, medication adherence is of particular

concern in low-and-middle-income countries (LMIC) like India, where accessibility and affordability issues are still pertinent.[3,15]

Barriers to adherence are often related to patient, medication, provider, and health system factors, with interactions between them.[16,17] Patient factors that influence adherence include poor health literacy, faulty cultural beliefs regarding medication effectiveness, and religious healing practices.[17] Low income, forgetting to take medication, and perceptions regarding pills like safety concerns, convenience, and necessity add to the above list. Inadequate knowledge about a drug and its use, not being convinced of the need for medication, fear of adverse effects, and long-term treatment regimens also prompt medication discontinuation.[15] Clinician factors includes: failure to recognize nonadherence, prescription of complex and multidrug regimens, ineffective communication of benefits of medications, and excluding patients in the treatment decision–making process.[17] Health system factors comprise limited insurance coverage, poor coordination of care between inpatient and outpatient settings, and inadequate communication between prescribers (i.e., specialists and primary care clinicians). In addition, the caregivers' aspects also become relevant in determining patients' adherence, as it is proven that CVD patients with caregivers are more likely to be adherent to medications.[18] Hence identifying patient-specific barriers and adopting suitable techniques to overcome them is imperative to improve medication adherence. A few successful facilitators that has helped us overcoming these barriers include: inclusion of medication counsellors into the continuum of care to guide patients, single-pill fixed-dose combinations, training pharmacists as coaches for drug therapies, building peer groups for chronic conditions, and developing information systems in the follow-up of patients.[19]

Quantitative studies have extensively studied medication adherence and its determinants. They do not, however, uncover life circumstances that may influence adherence from the patient perspective. A systematic review of qualitative studies will provide us with a better

understanding of the barriers and facilitators from the first-hand experiences of patients, healthcare providers, and caregivers.[20] Qualitative evidence synthesis, a novel research method, brings together the available qualitative evidence from primary studies through a systematic review process. Despite the conceptually rich evidence generated from primary qualitative studies, a qualitative evidence synthesis can aid policymakers and clinicians to get an overall insight of the findings, thereby enabling them to address all subtle and sensitive issues that most primary studies encounter. The findings from this qualitative evidence synthesis can guide various stakeholders to frame specific policy recommendations in non-communicable disease care. [21] Thus, we undertook this review to understand the perspective of various stakeholders (patients, caregivers, and healthcare providers) on the barriers and facilitators for medication adherence among CVD and DM patients in India. We also explored the suggestions and solutions provided by these stakeholders in overcoming the reported barriers.

METHODS

This review was performed by adhering to the "Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ)" statement. (Supplementary file 1) [22] We registered our protocol in the PROSPERO database (Registration number - CRD42020199529). We also searched PROSPERO and Cochrane to ensure that no similar review protocol has been reported. We also performed a preliminary search to ensure that no previous reviews of our similar topic targeting the Indian population were published.

Study design

We performed a qualitative evidence synthesis of all available qualitative studies on the barriers and facilitating factors for medication adherence among CVD and DM patients in India. This

review would help to aggregate the evidence of peer-reviewed articles and build an organized empirical research outline based on prior knowledge.

Eligibility criteria

Study type

We have included peer-reviewed qualitative studies conducted in India for our current review. Furthermore, qualitative evidence from other mixed methods studies was screened for eligibility and included in the qualitative component was relevant to our review. In addition, we included studies using qualitative techniques for data collection such as focussed group discussion (FGD), in-depth interviews (IDI), and Key Informant Interviews (KII).

Participant type

We have included the studies reporting the barriers and facilitators of medication adherence from patients' perspectives (CVD and DM), family members, healthcare workers (HCWs), or health system policymakers perspectives. HCWs were defined as per World health organisation (WHO) recommendation as "all the persons involved in the actions whose primary intent is to enhance the health."[23]

Outcome

The phenomenon of interest was to explore the barriers and facilitators for medication adherence among CVD and DM patients in India. We also explored the possible suggestions and solutions to address the barriers and improve compliance, as experienced by the patients, caregivers, family members, HCWs, and other relevant stakeholders.

Exclusion criteria

We have excluded the studies not available in English, books, conference abstracts, grey literature, or editorial comments. We have also excluded the studies reporting only quantitative data such as cross-sectional surveys, case-control, cohort studies, or intervention trials.

Search strategy

We have conducted a comprehensive and systematic search in databases and search engines such as Medline, Cochrane Library, ScienceDirect, and Google Scholar. A combination of medical subject heading (MeSH) and free-full text terms was used for carrying out a literature search. The detailed search strategy and search results in the databases mentioned above and search engines are provided in Supplementary File 2. In addition to this, we also checked the reference list of primary studies obtained via electronic search and included articles relevant to our review and analysis. The search was conducted in all above-mentioned databases from January 2010 to July 2020. Our search timeline was restricted to the past decade alone to ensure the identification of emerging issues.

Study selection process

Two investigators (YK and TR) independently performed the literature search, screened the title and abstract of all the identified studies, and retrieved the full text for articles relevant to our review. Further full-text screening of the retrieved articles was done again independently by the two investigators (YK, TR) to select the studies matching the eligibility criteria of our review. Disagreements during this process between the two investigators were resolved through consultation with a third investigator (SR).

Data Extraction and Management

After the study selection, two investigators (YK and TR) independently extracted the relevant data and study characteristics onto a predetermined data extraction format. Data entry was double-checked for accuracy by a third investigator (SR) by comparing the data presented in the review and individual study reports. As a result, we have extracted the following study characteristics: general information such as the name of the first author, the country in which the study was done, and year of publication, in the methods section, data collection period, study design, study participants, sample size, sampling technique, and data collection

procedure. In addition, barriers, facilitators, suggestions, and solutions to medication adherence were identified systematically.

Quality assessment

Two investigators (YK and SR) independently performed the quality check using the Critical Appraisal Skills Programme (CASP) criteria.[24] This checklist has been widely used for assessing the quality of studies included in Qualitative Evidence synthesis.[25] This checklist helps us to determine the coherence of included studies with the quality appraisal standard for qualitative studies. This checklist consists of 10 questions concerning the study's clarity, methodology, and results to rank the included studies. Subsequently, these studies were stratified into high quality (three stars for studies scoring 8 to 10 points), medium quality (two stars for studies scoring 4 to 7 points), and low rate (one star for studies scoring 0 to 3 points). We did not exclude the low-quality studies, but the interpretation of results was made with caution. Disagreements during the quality assessment process were resolved by discussion with the third investigator (TR).

Data Analysis

We analysed and reported the findings in separate clusters such as patients, caregivers, family members, HCWs, and policymakers to demonstrate the differences among these subgroups. We have adopted a thematic framework analysis to analyse and synthesize the data. Thematic framework analysis has been helpful as the evidence was primarily descriptive and improved our understanding of the barriers and facilitators in medication adherence among CVD and DM patients. This framework synthesis has five stages of synthesizing the qualitative data.

First stage - Familiarisation with the data: Primary investigator (YK) did the process of familiarisation with data by reviewing all the selected articles against the objective of our review and found the recurrent themes across the included studies.

The second stage - Identifying the thematic framework: The investigators used a predetermined thematic framework developed using literature to guide the thematic analysis. The final framework comprised of a detailed list of facilitators and barriers for medication adherence and also solutions to address the issue.

Third stage - Indexing: Two independent investigators (YK and SR) read the extracted information and searched for themes as per the predetermined thematic framework and found additional emerging themes. The framework underwent several revisions as and when a new theme emerged, after discussing with the entire team of investigators. Next, all the studies were completely read and examined till there was no new emergent theme. Coding of the data was then done as per the themes identified in our analysis. Finally, each preliminary study indexing was done using the codes related to the thematic framework. Whenever appropriate, sections of the studies were indexed with one or more codes.

Fourth stage - Charting: The investigators then sorted the data based on themes and presented these themes in the tabular format (chart). The rows and columns of the table indicate the themes related to the studies, which enabled us to compare the study findings across various themes and subthemes.

***Fifth stage - Mapping and interpretation*:** The investigators then used these charts to define the concepts identified, and finally mapped the nature and range of the phenomena. Our review explored the associations between the various emerging themes and helped in clarifying the findings. Finally, we mapped and interpreted the findings in line with our objectives and emergent themes.

Ethics Approval:

Approval from an ethics committee is not required since our review included only publicly available data without involving the human participants directly.

Patient and Public Involvement:

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Study selection

A comprehensive and systematic search was done to identify the relevant studies from January 2010 to July 2020. In total, we identified 1187 citations, and after the removal of duplicates from multiple databases, 982 records were screened for their title and abstract, and assessed for eligibility. From these records, we retrieved 33 articles, and after going through the full text of these articles, 18 studies were included in the review. (**Figure 1**).[26-43]

Characteristics of the studies included

Characteristics of the included studies are reported in **Table 1**. Of the 18 studies included, 9 (50%) were from the southern region, followed by 7 (38%) from the northern part of India. The mean age of the participants ranged from 25-76 years. The typology of the studies comprised of in-depth interviews (IDIs) and focussed group discussions (FGDs). The study participants were primarily patients with diabetes, hypertension, or any cardiovascular diseases (to explore the patient perspective), and health care workers (4 studies) providing care to them (to obtain the provider perspective). The total sample size of the included studies ranged from 6 to 100. The majority (10 of the included studies) were from the community, while the rest were either facility-based or had participants from ongoing trials. Four of the included studies used software for analysing the qualitative data, while the rest followed manual methods. Most of the included studies (14 out of 18) had high-quality evidence.

Narrative synthesis

Findings from our review showed that significant factors contributing to adherence were grouped under three themes: patient-related, family-related, and health system-related factors. The barriers, facilitators, and suggestions to improve medication adherence were summarized under these three themes.

Barriers in medication adherence

Table-2 shows the thematic framework analysis related to barriers in medication adherence among CVD and DM patients. All the 18 included studies have explored and reported on these barriers.

Patient-related factors

Significant patient-related barriers (10 studies) reported were lack of knowledge or understanding about the disease, its complications, and the treatment schedule, followed by forgetfulness to take medicines (7 studies). Reasons provided for the same were the patients' busy schedule, laziness, or forgetting to take the medication while travelling out-of-station. Patients have also reported certain misconceptions about the medicines like the risk of long-term neurological illness because of medication intake, inferior quality of drugs provided in hospitals, and wrong perception about stopping the medications once the patient feels normal. Patients in some studies have reported that they practice alternate systems of medicine such as herbal medicines and avoid taking allopathic medicines leading to poorer control. Substance use such as alcohol or tobacco use, side effects related to drugs, stress, and stigma were reported to be other barriers

Family-related factors

The patients and providers have reported lack of family support as a significant contributing factor for nonadherence. In addition, the lack of social and emotional support to the patients further promote nonadherence. Domestic works, personal priorities, commitments, or other family-related issues hinder the family members from adequate support.

Health system-related factors

In most of these studies, providers were also interviewed to understand the health system barriers responsible for nonadherence among CVD and DM patients. Healthcare providers and stakeholders interviewed, in almost all these studies, have reported affordability, accessibility, and acceptability as major factors hindering medication adherence. Affordability is of prime concern among patients seeking healthcare from private facilities. Though there are no direct medical costs involved in availing services from the public sector or primary healthcare centres, direct non-medical costs such as transport (due to poor accessibility) and indirect costs such as loss of wages (due to inconvenient consultation timing) were contributory. In addition, studies reported that patients, in general, had wrong perceptions about the quality of medications provided in public facilities, influencing them to choose private health facilities, including those belonging to lower socioeconomic status. Lack of risk communication, counselling, or empathy by the physicians mainly due to overburdened public health facilities and time constraints were the other health system-related barriers reported by the providers and patients.

Facilitators in medication adherence

Facilitators in medication adherence were also summarized using the pre-existing thematic framework (**Table-3**). In total, ten studies have explored the facilitators in medication adherence from the patient or providers' perspective.

Patient-related factors

Most of the studies (5 studies) reported fear of complications due to nonadherence and self-perception of being healthy (once they adhere to the medications) as the significant facilitators. In addition, having a reminder system in the form of reminder notebooks, separate pillboxes/cases/covers, or personalized shelf facilitates the patients in adhering to the medications. Some studies have also reported that integrating drug intake into daily routine activities and peer influence acts as good facilitators for compliance with medications.

Family-related factors

Family support was reported as a major facilitating factor for compliance with medication. Apart from the support, adverse experiences in the past, such as death or severe complications among the family members, instilled fear in the patients and making them more compliant to the medications.

Health system-related factors

Barriers reported in some of the studies, such as empathy and counselling by healthcare providers, were considered facilitators by other studies' patients. Another major facilitator from the health system side is the trust that patient has in their physician and their willingness to effectively follow advices related to self-care and adherence. Other familiar facilitators reported by the patients and providers were the use of dedicated pill cover/boxes for each drug provided in the clinic, linkage of health services with other non-governmental organisations (NGO) for provision of counselling and generating awareness, availability of medication, and use of polypills.

Suggestions to improve medication adherence

Suggestions and solutions to enhance the compliance to medication were reported in 16 out of the 18 included studies based on either patient or provider's perspective (**Table-4**). Few suggestions were related to patients and family members, while the majority were related to the change in the health system.

Patient and family-related factors

Creating or joining a peer support group was one among the major suggestions related to the patients. Digital reminder systems using a watch or a mobile phone were other uncommon suggestions to improve medication adherence.

Health system-related factors

Innovations in patient care, have been necessitated as an important factor to promote drug adherence. Some possible recommendations were hosting dedicated days for specific disease conditions to avoid overburdening the facilities, a dedicated counselling station for drug adherence during the clinic with separate human resources, and a unique pill dispensing mechanism like colour coding, etc were the other suggestions. In addition, information education and communication (IEC)/ behaviour change communication (BCC) campaigns, digitalizing the patient treatment records, linkage of healthcare services with NGOs or community-based organizations, regular training of healthcare workers, and promotion of polypill use were other common suggestions offered by the healthcare providers.

Discussion

We conducted this review to integrate qualitative evidence on barriers and facilitators for medication adherence among CVD and DM patients in India. We also further explored the suggestions to improve medication adherence. The studies included in our review involved a total of 636 participants (534 CVD and DM patients, 102 healthcare providers). The majority of the included studies were of high quality concerning study clarity, methodology, and results. We summarized the three major themes: barriers, facilitators, suggestions and reported our findings under the following four sub-themes: patients, care team, healthcare organization, and environment-related factors.

Comparison of findings with previous literature

Barriers in medication adherence

Major barriers were lack of patient's understanding about the disease and its complications, forgetfulness, and misconception about the medications. Lack of family support was seen as a major barrier from both patients' and providers' perspectives. In addition to these factors, stress and stigma were other contributory barriers. In addition to the above, adherence to medications was decided by patients' cultural beliefs, perceived discrimination, and social customs, which

are largely prevalent in a culturally influenced country like India. A few studies have also shown evidence of improvement in medication adherence in settings, where efforts were taken to overcome the cultural barriers. [44] We also found that the major health system-related barriers were lack of accessibility and availability, higher cost of medications, and poor physician attitude. These findings were in line with the previous review conducted among South-East Asian DM patients.[44-46] In addition, our findings of patients related factors were found to be similar to other patients belonging to non-English speaking Hispanic and south American ethnic groups, such as lack of understanding about their condition, along with additional stress and stigma.[47-49]

Facilitators in medication adherence

Fear of complications, self-perception of being healthy, having a reminder system were reported as major facilitators by patients. Physician trust, advice, empathy, and counselling were the common provider-related facilitators facilitating adherence. Common facilitators as reported by the patients and providers were: dedicated pill cover/boxes for each drug provided in the clinic, availability of medication, and use of polypills. These findings were also in line with the previous qualitative reviews conducted in low middle-income countries including India.[47-50]

Suggestions to improve medication adherence

The solutions provided by the patients and health professionals were in line with the barriers identified in our review. Comprehensive physician counselling to make the patients understand their own condition, complications of the disease and avoid misconception about the drugs and their side effects, along with good family support, and making the medication accessible and available free of cost were suggested as major suggestions to improve medication adherence. Similar interventions were also suggested by previous qualitative evidence on medication adherence among CVD and DM patients.[45-49] It is also interesting to note that medication

adherence was also hurdled by the patients' intention towards adherence, and this intention might vary across nations and cultural groups. The patient's intention not to refill prescriptions due to cost, not to take medication because he feels better, also influences the patient's decision. Thus future research exploring these reasons on patient's choice to adhere or not, rather than an inability to adhere (e.g., forgetting, no access) needs to be encouraged.

Strengths and limitations of the study

To the best of our knowledge, this is the first review synthesizing all possible qualitative factors associated with medication adherence among CVD and DM patients in India. We have provided comprehensive and systematic evidence on the barriers, facilitators related to medication adherence, adhering to the ENTREQ statement, thereby ensuring transparency and reproducibility. We examined this evidence through the lenses of a well-established theoretical framework model. Furthermore, our study was able to provide valuable suggestions to promote medication adherence from both patient's and provider's perspectives. In addition to these strengths, we found that the majority of the studies included in our review were of high quality evidence. This in turn ensures the transferability (external validity) of our review findings.

However, our review has certain limitations. We did not search grey literature, possibly missing some insights for our review. Hence, we cannot rule out the dissemination bias for an accurate and complete representation of medication adherence. We focussed primarily on the patient and provider perspective on medication adherence.[51] Hence, we cannot comment on the organizational or political influences on the adherence to long-term therapies as mentioned in the WHO report.[16] The sample size of the included studies can be considered relatively low (median sample size - 30). However, all the studies were conducted till the achievement of data saturation. In addition to the above, these results and suggestions need to be considered after taking into account India's cross-cultural adaptations, customs, linguistic variations, and genetic susceptibility, and higher prevalence of risk factor profile.

Implications for clinical and public health practice

Improving medication adherence is essential to achieve better control and prevent life-threatening complications. Factors related to patients such as self-awareness and fear about the condition and its complications acted as a major facilitator for medication adherence. We also observed that most of the barriers identified were modifiable, in nature. Interventions should focus on these modifiable barriers such as knowledge barriers, intention barriers, and health system-related barriers to achieve better adherence. In addition, the family members need to help the patients in mapping their daily routine and link the medicine intake with these routines to facilitate adherence. Our review also suggested that healthcare providers play an important role in promoting medication adherence. Hence, the interventions should not only target the patients but also the family members and healthcare providers and they should be tailored to suit differences in setting, culture, and type of the patients.

Implications for future research

More evidence needs to be generated concerning the effectiveness and feasibility of possible solutions obtained in our review including the digital solutions, polypills, peer support groups, etc. Further qualitative studies including the subgroup of patients with CVD and DM under different stages and treatment regimens are required to contextualize the medication adherence on a larger scale. Exploring the barriers using a theoretical framework with the same methodological approach, can provide more reliable evidence to develop patient-centred interventions and achieve better control among CVD and DM patients.

Conclusion:

In our review, we categorised the facilitating factors and barriers influencing medication adherence into patient-related, health system-related, and care team-related factors. Thus, we advocate the creation of peer support groups, use of a digital reminder system for overcoming patients related factors, and integration of Indian systems of medicine, physiotherapy, and

geriatric clinics even at the primary healthcare level for overcoming the health system-related barriers towards medication adherence.

Funding: None

Competing interests statement: None declared

Acknowledgements: None

Author contribution statement: Conceived and designed the study: YK & SR, Data management and extraction: YK, SR & TR, Analysed the data and wrote the paper: SR, YK & TR. Provided comments and inputs to revise the manuscript: SR, YK, TR & MT

Data sharing statement: The authors confirm that the data supporting the findings of this study are available within the article

References:

1. Walker IF, Garbe F, Wright J, Newell I, Athiraman N, Khan N, et al. The Economic Costs of Cardiovascular Disease, Diabetes Mellitus, and Associated Complications in South Asia: A Systematic Review. Value Health Reg Issues. 2018;15:12–26.
2. Glovaci D, Fan W, Wong ND. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. Curr Cardiol Rep. 2019;21:21.
3. Prabhakaran D, Jeemon P, Sharma M, Roth GA, Johnson C, Harikrishnan S, et al. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018;6:e1339–51.
4. Tandon N, Anjana RM, Mohan V, Kaur T, Afshin A, Ong K, et al. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018;6:e1352–62.

5. Durand H, Hayes P, Morrissey EC, Newell J, Casey M, Murphy AW, et al. Medication adherence among patients with apparent treatment-resistant hypertension: systematic review and meta-analysis. J Hypertens. 2017;35:2346–57.
6. Polypharmacy and Medication Adherence in Patients With Type 2 Diabetes | Diabetes Care [Internet]. [cited 2020 Jul 30]. Available from: https://care.diabetesjournals.org/content/26/5/1408.short
7. Vrijens B, Antoniou S, Burnier M, de la Sierra A, Volpe M. Current Situation of Medication Adherence in Hypertension. Front Pharmacol [Internet]. 2017 [cited 2020 Jul 31];8. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2017.00100/full
8. Rehman T, Rajaa S, Kumar G, Jayalakshmy R. Prevalence and factors influencing diabesity among persons with type 2 diabetes mellitus in urban Puducherry: A cross-sectional analytical study. Indian J Community Med. 2020 Jul;45(3):315.
9. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence. 2016;10:1299–307.
10. Leporini C, De Sarro G, Russo E. Adherence to therapy and adverse drug reactions: is there a link? Expert Opin Drug Saf. 2014;13 Suppl 1:S41-55.
11. Lam WY, Fresco P. Medication Adherence Measures: An Overview. BioMed Res Int. 2015; 2015:1–12.
12. Kvarnström K, Airaksinen M, Liira H. Barriers and facilitators to medication adherence: a qualitative study with general practitioners. BMJ Open. 2018;8:e015332.
13. Ferdinand KC, Senatore FF, Clayton-Jeter H, Cryer DR, Lewin JC, Nasser SA, et al. Improving Medication Adherence in Cardiometabolic Disease. J Am Coll Cardiol. 2017;69:437–51.

14. Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. Adv Ther. 2005;22:313–56.
15. Dennis T, Meera NK, Binny K, Sekhar MS, Kishore G, Sasidharan S. Medication adherence and associated barriers in hypertension management in India. CVD Prev Control. 2011 Jan 1;6(1):9-13.
16. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. Circulation. 1997;95:1085–90.
17. WHO | ADHERENCE TO LONG-TERM THERAPIES: EVIDENCE FOR ACTION [Internet]. WHO. World Health Organization; [cited 2020 Jul 30]. Available from: http://www.who.int/chp/knowledge/publications/adherence_report/en/
18. Aggarwal B, Liao M, Mosca L. Medication Adherence Is Associated with Having a Caregiver Among Cardiac Patients. Ann Behav Med Publ Soc Behav Med. 2013;46:237–42.
19. Daliri S, Bekker CL, Buurman BM, Scholte op Reimer WJM, van den Bemt BJF, Karapinar – Çarkit F. Barriers and facilitators with medication use during the transition from hospital to home: a qualitative study among patients. BMC Health Serv Res. 2019; 19:204.
20. Rathbone AP, Todd A, Jamie K, Bonam M, Banks L, Husband AK. A systematic review and thematic synthesis of patients' experience of medicines adherence. Res Social Admin Pharm. 2017 May 1;13(3):403-39.
21. Flemming K, Booth A, Garside R, Tunçalp Ö, Noyes J. Qualitative evidence synthesis for complex interventions and guideline development: clarification of the purpose, designs and relevant methods. BMJ Global Health. 2019 Jan 1;4(Suppl 1):e000882.

22. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012; 12:181

23. Mohanty A, Kabi A, Mohanty AP. Health problems in healthcare workers: A review. J Family Med Primary Care. 2019 Aug;8(8):2568.

24. Critical Appraisal Skills Programme (2018). CASP (Qualitative) Checklist. [online] Available at: https://casp-uk.net/wp-content/uploads/2018/01/CASP-Qualitative-Checklist-2018.pdf Accessed: 12 September 2020

25. Booth A, Noyes J, Flemming K, Gerhardus A, Wahlster P, van der Wilt GJ,et al. Structured methodology review identified seven (RETREAT) criteria for selecting qualitative evidence synthesis approaches. J Clin Epidemiol. 2018 Jul 1;99:41-52.

26. Agarwal A, Davies D, Goenka S, Prabhakaran D, Huffman MD, Mohanan PP. Facilitators and barriers of heart failure care in Kerala, India: A qualitative analysis of healthcare providers and administrators. Indian Heart J. 2019; 71(3):235–41.

27. Dhar L. Perceptions of global coronary heart disease risk, and adherence to antihypertensive treatment among low income urban women in Delhi, India (Doctoral dissertation, Curtin University).

28. George CE, Ramadas D, Norman G, Mukherjee D, Rao T. Barriers to cardiovascular disease risk reduction: Does physicians' perspective matter? Indian Heart J. 2016; 68(3):278–85

29. Gupta S, Dhamija JP, Mohan I, Gupta R. Qualitative Study of Barriers to Adherence to Antihypertensive Medication among Rural Women in India. Int J Hypertens. 2019; 2019:1–7.

30. Gupta S, Virk A, Mittal A, Agarwal B. Patterns and determinants of healthcare-seeking behavior among hypertensive patients in a rural population of north India: A mixed-method study. J Family Med Prim Care. 2020; 9(6):2830

31. Jayanna K, Swaroop N, Kar A, Ramanaik S, Pati MK, Pujar A, et al. Designing a comprehensive Non-Communicable Diseases (NCD) programme for hypertension and diabetes at primary health care level: evidence and experience from urban Karnataka, South India. BMC Public Health. 2019; 19:1

32. Krishnamoorthy Y, Giriyappa DK, Eliyas SK, Priyan S, Saya GK, Lakshminarayanan S. Patient and Provider's Experience and Perspective in Addressing Barriers to Medication Adherence Among Noncommunicable Disease Patients in Rural Puducherry, South India—A Qualitative Study. J Patient Exp. 2019; 6(3):216–23

33. Kusuma YS. Migrants' Perceptions on Barriers to Treatment Seeking for Hypertension: A Qualitative Study from Delhi, India. Studies on Ethno-Medicine. 2010; 4(3):173–6

34. Miller V, Nambiar L, Saxena M, Leong D, Banerjee A et al. Exploring the barriers to and facilitators of using evidence-based drugs in the secondary prevention of cardiovascular diseases: findings from a multistakeholder, qualitative analysis. Global Heart. 2018; 13(1):27-34.

35. Newtonraj A, Arun S, Bazroy J, Tovia S. Lay perspectives on causes and complications of hypertension; and barrier to access health care by known hypertensive patients: a qualitative study from a rural area of South India. Int J Community Med Public Health. 2017; 4(3):704

36. Nimesh VV, Halder A, Mitra A, Kumar S, Joshi A, Joshi R, et al. Patterns of healthcare seeking behavior among persons with diabetes in Central India: A mixed method study. J Family Med Prim Care. 2019; 8(2):677.

37. Pati S, Van den Akker M, Schellevis FF, Sahoo K, Burgers JS. Managing diabetes mellitus with comorbidities in primary healthcare facilities: a qualitative study among physicians in Odisha, India. 2020. Research square [preprint] doi: 10.21203/rs.3.rs-22272/v1

38. Anitha Rani M, Shriraam V. Are Patients With Type 2 Diabetes Not Aware or Are They Unable to Practice Self-Care? A Qualitative Study in Rural South India. J Prim Care Community Health. 2019; 10:2150132719865820.

39. Salam A, Praveen D, Patel A, Tewari A, Webster R. Barriers and facilitators to the use of cardiovascular fixed-dose combination medication (polypills) in Andhra Pradesh, India: a mixed-methods study. Global Heart. 2019; 14(3):303-10.

40. Satish P, Khetan A, Barbhaya D, Agarwal M, Mohan SK, Josephson R, Webel AR. A qualitative study of facilitators and barriers to cardiovascular risk factor control in a semiurban population in India. J Family Med Prim Care. 2019; 8(12):3773-3778.

41. Thakur JS, Vijayvergiya R, Jaswal N, Ginsburg A. Assessment and barriers to medication adherence for secondary prevention of cardiovascular disease among patients with coronary artery disease in Chandigarh, India. Int J Non-Commun Dis. 2016;1:37-41.

42. Venkatesan M, Dongre AR, Ganapathy K. A community-based study on diabetes medication nonadherence and its risk factors in rural Tamil Nadu. Indian J Community Med. 2018; 43(2):72-76

43. Wood F, Salam A, Singh K, Day S, Jan S, Prabhakaran D, et al. Process evaluation of the impact and acceptability of a polypill for prevention of cardiovascular disease. BMJ Open. 2015; 5(9):e008018

44. Saha S, Korthuis PT, Cohn JA, Sharp VL, Moore RD, Beach MC. Primary care provider cultural competence and racial disparities in HIV care and outcomes. J Gen Intern Med. 2013;28(5):622-9. https://doi. org/10.1007/s11606-012-2298-8.

45. Sohal T, Sohal P, King-Shier KM, Khan NA. Barriers and Facilitators for Type-2 Diabetes Management in South Asians: A Systematic Review. PLoS ONE. 2015; 10(9): e0136202.

46. Sears K, Scobie A, MacKinnon NJ. Patient-related risk factors for self-reported medication errors in hospital and community settings in 8 countries. Can Pharm J: Revue des Pharmaciens du Canada. 2012 Mar;145(2):88-93.

47. Nam S, Chesla C, Stotts NA, Kroon L, Janson SL. Barriers to diabetes management: patient and provider factors. Diabetes Res Clin Pract. 2011; 93(1):1–9

48. Lipton RB, Losey LM, Giachello A, Mendez J, Girotti MH. Attitudes and issues in treating Latino patients with type 2 diabetes: views of healthcare providers. Diabetes Educ. 1998; 24: 67–71

49. Sridharan SG, Chittem M, Maya S. Patients' Experiences of Barriers and Facilitators for Adherence to Type 2 Diabetes Mellitus: A Meta-Ethnography. Journal of Social Health and Diabetes. 2019 Dec;7(02):61-72.

50. Al Hamid A, Ghaleb M, Aljadhey H, et al. A systematic review of qualitative research on the contributory factors leading to medicine-related problems from the perspectives of adult patients with cardiovascular diseases and diabetes mellitus. BMJ Open 2014; 4:e005992.

51. Toews I, Booth A, Berg RC et al. Further exploration of dissemination bias in qualitative research required to facilitate assessment within qualitative evidence synthesis. J Clin Epidemiol 2017; 88:133–139

Figure 1: Flow chart showing the search strategy and selection of studies

Table 1: Characteristics of the studies included (N=18)

S.No	Author and year	State	Data collection method	Study participants	Study setting	Approach	Coding	Theoretical framework used	Method of analysis	Sample size	Mean Age in years	Study quality
1.	Agarwal 2019	Kerala	IDI	Clinical and administrative staff	Facility based	NR	Inductive	NR	Dedoose Software	21	NR	***
2.	Dhar et al 2016	Delhi	IDI	Hypertensive women aged 35-59 years	Community based	NR	Inductive	Yes	Manual content analysis	30	48	***
3.	George et al 2016	Karnataka	IDI	Physicians providing Non communicable disease care	Community based	NR	Inductive	NR	Manual content analysis	36	46	***
4.	Gupta et al 2019	Rajasthan	IDI	Hypertensive women	Facility based	NR	NR	NR	Manual content analysis	30	56	**
5.	Gupta et al 2020	Haryana	IDI	Hypertension patients	Facility based	NR	NR	NR	Manual content analysis	100	38-76	***
6.	Jayanna et al 2019	Karnataka	IDI & FGD	Diabetes and Hypertension patients	Facility based	NR	NR	Yes	Manual content analysis	10 IDI + 20 FGDs	NR	***
7.	Krishnamoorthy et al 2018	Puducherry	IDI & KII	Diabetes and Hypertension patients & Healthcare workers	Community based	NR	Inductive	NR	Manual content analysis	6 IDI + 4 KII	NR	***
8.	Kusuma et al 2010	Delhi	KII & FGD	Recent and Settled Migrants having hypertension inhabited in Delhi	Community based	NR	NR	NR	Manual content analysis	14 (KII) + 20 (FGD)	38 – 50 (KII) & 25 – 40 (FGD)	***
9.	Miller et al 2017	Delhi	IDI	Cardiovascular disease patients	Trial based	Descriptive	NR	NR	Manual content analysis	14	NR	***
10.	Newtonraj et al 2017	Tamil Nadu	Personal interviews	Hypertensive patients	Community based	NR	NR	NR	Manual content analysis	40	NR	**

11.	Nimesh et al 2019	Madhya Pradesh	IDI	Individuals with diabetes	Community based	NR	Inductive	Yes	Manual content analysis	60	52	***
12.	Patti et al 2020	Orissa	IDI	Primary care physicians	Facility based	NR	NR	NR	Manual content analysis	17	40	***
13.	Rani et al 2019	Tamil Nadu	FGD	Individuals with diabetes	Community based	Descriptive	NR	NR	Manual content analysis	50	50	**
14.	Salaam et al 2019	Andhra Pradesh	IDI	Patients with Cardiovascular disease	Community based	NR	NR	Yes	NVivo version 11 software	12	62	***
15.	Satish et al 2019	West Bengal	FGD	Patients with hypertension and/or diabetes	Trial based	NR	NR	Yes	Manual content analysis	70	53	***
16.	Thakur et al 2016	Chandigarh	IDI & FGD	Coronary artery disease patients	Facility based	NR	NR	NR	Manual Thematic analysis	20	NR	*
17.	Venkatesan et al 2018	Tamil Nadu	IDI	Health care workers	Community based	NR	NR	NR	Anthropac software	10	NR	***
18.	Wood et al 2015	Hyderabad and Delhi	IDI	Patients with Cardiovascular diseases	Trial based	NR	NR	Yes	NVivo software	52	57	***

NR – Not Reported
IDI – In depth Interview
FGD – Focussed Group Discussion
KII – Key informant interview

Table 2: Thematic framework analysis for summarizing barriers in medication adherence experienced by CVD & DM patients in India

Main theme/Sub-themes	Barriers in Medication Adherence	Studies
PATIENTS	1. **Lack of awareness/knowledge:** Lack of knowledge and understanding about the disease, its complications and treatment among the patients	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Newtonraj et al 2017, Patti et al 2020, Tan et al 2017, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	2. Forgetfulness: Patients forget to take medicine because of busy schedule	**Dhar et al 2016, Gupta et al 2019, Gupta et al 2020, Rani et al 2019, Venkatesan et al 2018, Wood et al 2015, Tan et al 2017, Thakur et al 2016**
	3. Misconception about medications: Patient has wrong perception about the medications, especially about its side effects and quality	**George et al 2016, Gupta et al 2020, Patti et al 2020, Rani et al 2019, Salaam et al 2019, Tan et al 2017, Venkatesan et al 2018**
	4. Preference to alternate system of medicine: Patients prefers taking herbal and other alternate system of medicines for their condition	**George et al 2016, Tan et al 2017, Venkatesan et al 2018**
	5. Ill effects of substance abuse: Patients have difficulty in adhering to medications during the bout of tobacco or alcohol consumption	**Jayanna et al 2019, Krishnamoorthy et al 2018**
	6. Effect of side effects: Patients stop their medication once they develop side effects related to the drugs	**Venkatesan et al 2018, Wood et al 2015**
	7. Stress: Patients developing stress due to personal or work-related problems are more non-adherent to medications	**Krishnamoorthy et al 2018**
	8. Stigma: Patients feel stigmatised in revealing their disease status to other family/friends leading to lack of support from them	**Krishnamoorthy et al 2018**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Family support:** Lack of physical, emotional and social support as the family members are pre-occupied with domestic works, crisis, other priorities and commitments	**Dhar et al 2016, George et al 2016, Gupta et al 2020, Krishnamoorthy et al 2018, Kusuma et al 2010, Newtonraj et al 2017, Rani et al 2019, Wood et al 2015**
	2. Risk communication: Poor risk communication or counselling to patients and family members about non-adherence to medication by the treating physicians	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Thakur et al 2016**
	3. Physician attitude: Lack of respect, empathy, communication and attention towards patients by the treating physicians	**Dhar et al 2016, Gupta et al 2019, Kusuma et al 2010, Jayanna et al 2019**

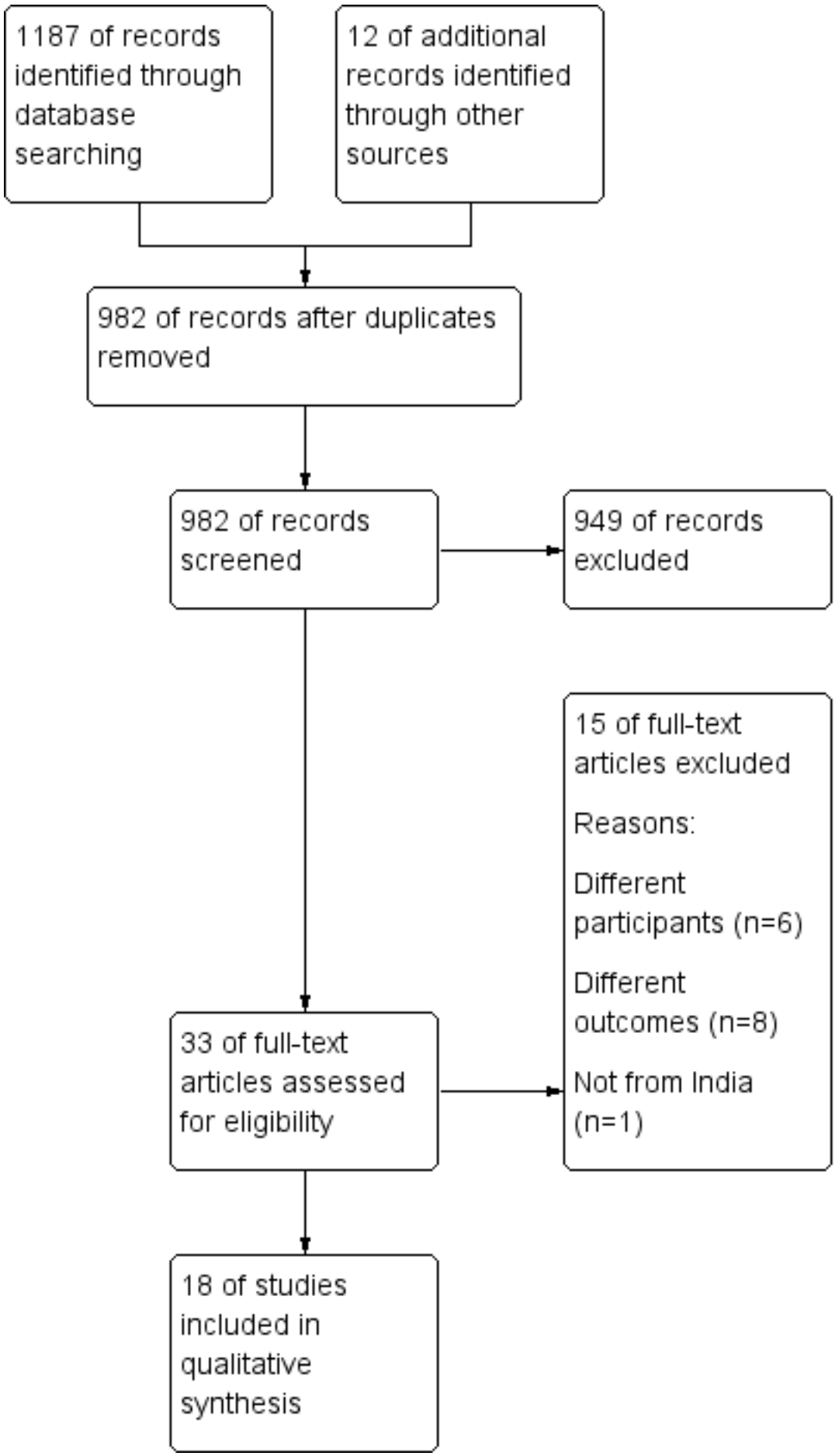
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Affordability:** Patients lose their daily wages due to inconvenient consultation timings in public facilities, which is aggravated by travel costs due to poor access, and higher medication costs while preferring private facilities	**Agarwal et al 2019, Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Kusuma et al 2010, Miller et al 2017, Nimesh et al 2019, Salaam et al 2019, Satish et al 2019, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	2. Accessibility: Lack of access to healthcare facilities (more distance) requiring longer travel and waiting time.	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Miller et al 2017, Newtonraj et al 2017, Tan et al 2017, Thakur et al 2016, Venkatesan et al 2018, Wood et al 2015**
	3. Availability: Non-availability of essential medicines in public healthcare facilities	**Dhar et al 2016, Jayanna et al 2019, Kusuma et al 2010, Miller et al 2017, Newtonraj et al 2017, Patti et al 2020, Salaam et al 2019, Wood et al 2015**
	4. Acceptability: Medications from public health facilities are not acceptable to the patients due to poorer quality	
	5. Overburdening of primary health centres: Burdening of primary health facilities lead to time constraints in patient counselling regarding medication adherence	**Jayanna et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Patti et al 2020, Venkatesan et al 2018**

Table 3: Thematic framework for summarizing facilitators in medication adherence experienced by CVD & DM patients in India

Main theme/Sub-themes	Facilitators in Medication Adherence	Studies
PATIENTS	**1. Self-awareness and fear:** Patient's understanding about medicine adherence and fear about complications of non-adherence keeps them healthy	**Krishnamoorthy et al 2018, Miller et al 2017, Patti et al 2020, Satish et al 2019, Tan et al 2017, Wood et al 2015**
	2. Medicine Reminder system: Separate pill boxes/cases/covers, personalized shelf, and maintaining drug record notebook helps them in remembering daily doses	**Dhar et al 2016, Krishnamoorthy et al 2018, Miller et al 2017, Tan et al 2017**
	3. Integrating drug intake with the daily routine: Fixed time for medicine intake, separate place for keeping drug, and making arrangements during travel helps them in adherence	**Dhar et al 2016, Krishnamoorthy et al 2018**
	4. Positive peer influence: Good adherence to medication by the patient's peers motivates the patient to be compliance to their own drug intake	**Gupta et al 2019, Krishnamoorthy et al 2018**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Family support**: Constant reminders by family members for drug intake	**Dhar et al 2016, Gupta et al 2020, Krishnamoorthy et al 2018, Miller et al 2017, Wood et al 2015**
	2. Past adverse experiences: Death of patients' own family members due to complications of the condition has motivated them to adhere to medication	**Dhar et al 2016, Krishnamoorthy et al 2018**
	3. Healthcare provider counselling and empathy: Patients described that counselling from their healthcare providers has motivated them to remain adherent	**Kusuma et al 2010, Miller et al 2017, Patti et al 2020, Salaam et al 2019, Tan et al 2017**
	4. Trust in physician: Adherence is more when a positive rapport and trust is established between the patient and health care providers.	**Dhar et al 2016, Krishnamoorthy et al 2018, Satish et al 2019**
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Dedicated pill boxes/covers:** Provision of different medications in separate boxes/covers in the healthcare facility has helped as the patient to remember which medication to take at what time	**Krishnamoorthy et al 2018, Wood et al 2015**
	2. Combination drugs (polypills): Polypills had the following advantages to facilitate the medication adherence: a smaller number of pills, lower frequency, less chance of forgetting, potential for lower cost, and convenient simpler regimen	**Salaam et al 2019, Wood et al 2015**
	3. Availability of medications: Proper pharmacy inventory control and stock delivery has aided in medication adherence	**Miller et al 2017**
ENVIRONMENT (Regulatory, market and policy framework)	**1. NGO Support**: Patients has reported that sharing their concerns and receiving counselling from NGO/ Health officers acted as a facilitator for drug intake	**Tan et al 2017, Wood et al 2015**

Table 4: Thematic framework for summarizing suggestions to improve medication adherence among CVD & DM patients in India

Main theme/Sub-themes	Suggestions to improve medication adherence	Studies
PATIENTS	**1. Peer support groups:** Patients can motivate each other by forming support groups among themselves	**Krishnamoorthy et al 2018**
	2. Digital reminder system: Patient can use digital reminders such as watch, mobile phone to adhere to their drug schedule	**Krishnamoorthy et al 2018, Miller et al 2017**
CARE TEAM (Frontline care providers - Healthcare professionals, family members and others)	**1. Social support:** Family members can be educated and asked to provide support by reinforcing compliance, reminding about drug intake, motivating them patients to avoid substance abuse	**Agarwal et al 2019, Dhar et al 2016, Krishnamoorthy et al 2018, Nimesh et al 2019, Wood et al 2015**
	2. Financial support: Family members can provide financial support to cover the cost of medications, travel etc.	**Gupta et al 2019**
	3. Regular training of healthcare workers: Physicians and other healthcare workers involved in prescribing drugs and counselling should undergo regular training on standard treatment protocols	**George et al 2016, Jayanna et al 2019, Miller et al 2017, Patti et al 2020, Satish et al 2019**
	4. Team work approach: Integration of AYUSH, mental health counsellors, physiotherapist and geriatric clinics at primary healthcare level	**George et al 2016, Miller et al 2017, Patti et al 2020**
HEALTHCARE ORGANIZATION (Infrastructure/Resources)	**1. Innovations in patient care:** Healthcare workers can make innovations like dedicated day for specific conditions (diabetes day, etc), dedicated counselling station/session with additional staff for detailing the importance of adherence and complications related to non-adherence, unique pill dispensing mechanism (colour coding)	**Agarwal et al 2019, Dhar et al 2016, Jayanna et al 2019, Krishnamoorthy et al 2018, Miller et al 2017, Newtonraj et al 2017, Patti et al 2020, Satish et al 2019, Venkatesan et al 2018, Wood et al 2015**
	2. IEC/BCC/Awareness campaigns: Putting up of IEC materials and conducting campaigns on importance of adherence in public places and workplaces	**Dhar et al 2016, George et al 2016, Gupta et al 2019, Gupta et al 2020, Jayanna et al 2019, Krishnamoorthy et al 2018, Newtonraj et al 2017, Patti et al 2020, Rani et al 2019**
	3. Digitalizing patient treatment record: Digitalizing a dedicated treatment record for each patient can help in better follow-up of the patient and improve adherence	**Jayanna et al 2019, Miller et al 2017, Patti et al 2020, Satish et al 2019, Wood et al 2015**
	4. Polypills: Disseminating the advantages of polypills to healthcare professionals by CME/conferences and patients by public education campaigns; Integration of polypills into clinical practice. etc	**Salaam et al 2019, Wood et al 2015**
ENVIRONMENT (Regulatory, market and policy framework)	**1. Linkage of health services with NGO and community-based organizations:** Community members, volunteers, anganwadi workers, self-help groups and NGO workers can be trained in counselling the patients to improve medication adherence	**Dhar et al 2016, Jayanna et al 2019, Krishnamoorthy et al 2018, Kusuma et al 2010, Miller et al 2017, Tan et al 2017**


1187 of records identified through database searching
12 of additional records identified through other sources
982 of records after duplicates removed
982 of records screened
949 of records excluded
15 of full-text articles excluded
Reasons:
Different participants (n=6)
Different outcomes (n=8)
Not from India (n=1)
33 of full-text articles assessed for eligibility
18 of studies included in qualitative synthesis

Supplementary file 1. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ Checklist (Tong, *et al.*, 2012)

Item No.	Guide and Description	Report Location
1. Aim	State the research question the synthesis addresses	P 6, 1-13
2. Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology (e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis)	P9, 16-25 P10, 1-22
3. Approach to searching	Indicate whether the search was pre-planned (comprehensive search strategies to seek all available studies) or iterative (to seek all available concepts until they theoretical saturation is achieved)	P8, 1-10
4. Inclusion criteria	Specify the inclusion/exclusion criteria (e.g. in terms of population, language, year limits, type of publication, study type)	P7, 3-23
5. Data sources	Describe the information sources used (e.g. electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists) and when the searches conducted; provide the rationale for using the data sources	P8, 1-10
6. Electronic Search strategy	Describe the literature search (e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits)	Supplementary file 1
7. Study screening methods	Describe the process of study screening and sifting (e.g. title, abstract and full text review, number of independent reviewers who screened studies)	Figure 1
8. Study characteristics	Present the characteristics of the included studies (e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions)	Table 1
9. Study selection results	Identify the number of studies screened and provide reasons for study exclusion (e.g. for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications to the research question and/or contribution to theory development)	Fig 1 - PRISMA flow diagram P11, 6-18
10. Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings (e.g. assessment of conduct (validity and robustness),	P11, 14-18 Table 1

	assessment of reporting (transparency), assessment of content and utility of the findings)	
11. Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings (e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope [25]; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and interpretations, reporting)	P9, 3-14 Table 1
12. Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required	P8, 11-17
13. Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale	P11, 14-18 Table 1
14. Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? (e.g. all text under the headings "results /conclusions" were extracted electronically and entered into a computer software)	P8, 18-25
15. Software	State the computer software used, if any	None used
16. Number of reviewers	Identify who was involved in coding and analysis	P9, 16-22
17. Coding	Describe the process for coding of data (e.g. line by line coding to search for concepts)	P9, 23-35 P10, 1-22
18. Study comparison	Describe how were comparisons made within and across studies (e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary)	Table 2
19. Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive	Inductive process Table 2
20. Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation	Table 2
21. Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct)	P11-14

Supplementary Table 2: Detailed search strategy

Key word	Alternative word
Qualitative studies	((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms] Case studies OR Focused group discussions OR phenomenological studies OR ethnographic studies OR interviews))
Medication Adherence	((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms])
Barriers, Facilitators and solutions	Challenges OR Challenge OR Problem OR Problems barriers OR Difficulties OR Issues OR Limitations OR Obstacles OR Facilitators OR Suggestions OR Solutions
Diabetes mellitus and CVDs	((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms] OR Coronary Disease[MeSH Terms] OR Coronary Artery Disease[MeSH Terms] OR Heart Diseases[MeSH Terms] OR Cerebrovascular Diseases[MeSH Terms] OR Stroke[MeSH Terms]))

India	(India[MeSH Terms] OR Republic of India[MeSH Terms]))

Search results (PubMed):

((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms])) AND ((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms]) OR Life Change Events[MeSH Terms]) OR Trust[MeSH Terms]))) AND ((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms])) AND (India[MeSH Terms] OR Republic of India[MeSH Terms])) – 199 (Filters: Years between 2010 and 2020 and English language publication)

((((((((((((Qualitative Research[MeSH Terms]) OR Focus Groups[MeSH Terms]) OR Anthropology, Cultural[MeSH Terms]) OR Ethnopsychology[MeSH Terms]) OR Grounded Theory[MeSH Terms]) OR Nursing Methodology Research[MeSH Terms]) OR Narrative Medicine[MeSH Terms]) OR Tape Recording[MeSH Terms]) OR Culture[MeSH Terms]) OR Attitude[MeSH Terms] Case studies OR Focused group discussions OR phenomenological studies OR ethnographic studies OR interviews))) AND ((((((((((((((((((Medication Adherence[MeSH Terms]) OR Patient Compliance[MeSH Terms]) OR No-Show Patients[MeSH Terms]) OR Health Personnel[MeSH Terms]) OR drug effects [Subheading]) OR (Treatment Adherence[MeSH Terms] OR Compliance[MeSH Terms])) OR Self Medication[MeSH Terms]) OR Self Administration[MeSH Terms]) OR Patient Medication Knowledge[MeSH Terms]) OR Attitude to Health[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms])) OR Patient Preference[MeSH Terms]) OR Patient Acceptance of Health Care[MeSH Terms]) OR Motivation[MeSH Terms]))) AND (Challenges OR Challenge OR Problem OR Problems barriers OR Difficulties OR Issues OR Limitations OR Obstacles OR Facilitators OR Suggestions OR Solutions)) AND (((((((Diabetes Mellitus[MeSH Terms]) OR Cardiovascular Diseases[MeSH Terms] OR Hypertension[MeSH Terms] OR Coronary Disease[MeSH Terms] OR Coronary Artery Disease[MeSH Terms] OR Heart Diseases[MeSH Terms] OR Cerebrovascular Diseases[MeSH Terms] OR Stroke[MeSH Terms]))))) AND ((India[MeSH Terms] OR Republic of India[MeSH Terms]))) – 31 results (Filters: Years between 2010 and 2020 and English language publication)

Google scholar: 635 + 22 + 6 + 12 = 675

ScienceDirect: (Diabetes Mellitus OR Cardiovascular Diseases OR Hypertension) AND (Qualitative Study OR Qualitative) AND (India) AND (Adherence) – 238 articles

Cochrane library: (Diabetes Mellitus OR Cardiovascular Diseases OR Hypertension) AND (Qualitative Study OR Qualitative) AND (India) AND (Adherence) – 34 articles