

# Prevalence, Barriers, and Interventions related to Medication Adherence Among Patients Diagnosed with Major Depressive Disorder: A Scoping Review

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## Abstract

Background: Adherence to psychotropic medication is still a concern to health care systems, mental healthcare professionals, researchers, and patients, as well. Recent literature on medication adherence increased focusing on the pervasiveness and significant impacts of adherence to medications. Purpose: The purpose of this scoping review is to identify the prevalence, contributing factors, methods of measurement, and interventions related to medication adherence among patients diagnosed with Major Depressive Disorders (MDD). Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guideline was used. The scoping review involves the review, analysis, and synthesis of a broad scope of literature. Results: A total of 36 articles met the inclusion criteria for this scoping review. The prevalence of medication adherence among patients diagnosed with MDD ranged from 10.6% to 85.4%. About 67% of studies used self-reports as methods of data collection. Illness-related factors (e.g., the onset of the illness, duration of illness, symptoms, and illness severity), medication-related factors (e.g., adverse reactions, duration of treatment, cost of treatment), and patient-related factors (e.g., beliefs, attitudes, knowledge, self-stigma) were the most reported factors to associate with medications adherence. Also, the multi-faceted intervention has been recommended over a single-element intervention to enhance medication adherence. Conclusion: There is a need to select and integrate good assessment measures of medication adherence, which lead to providing better evidence on the outcomes, risk factors, and interventions to improve medication adherence.

## Introduction

Despite decades of researches, adherence to medication is still a widely acknowledged and persistent concern for the health care systems, healthcare professionals, researchers, and patients, as well.<sup>1</sup> The increased literature on medication adherence has focused primarily on the pervasiveness and significant impact of adherence to medications on healthcare outcomes.<sup>2</sup> According to World Health Organization (WHO), medication adherence is defined as “the extent to which a person’s behaviour-taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”.<sup>3</sup> While adherence acknowledged benefits and positive impacts on the health of patients, nonadherence medication has been reported to cause multiple forms of negative healthcare outcomes.<sup>4</sup> In general, an overabundance of the literature suggests that patients do not adhered strictly to the drug regimen as recommended by their primary care providers.<sup>5</sup>

Although medication adherence introduced as a core function of care providers in education and discharge planning, nonadherence to medications is widely observed, causing negative healthcare outcomes and poor prognosis, in particular, among patients with chronic diseases.<sup>6</sup> According to Jafari Oori et al<sup>5</sup>, 50% of patients with chronic illnesses have poor medication adherence. Recent studies across multiple chronic conditions reported that nonadherence to medication range from 7.5% to 96%.<sup>6-8</sup> For patients suffering from

psychiatric disorders, nonadherence has been reported with more significant figures. For example, Gebeyehu and colleagues<sup>9</sup> reported that 55% of patients with psychiatric disorders have a high level of medication nonadherence inferring poor prognosis and early relapse.

Depressive disorders are the most common psychiatric conditions affecting 300 million around the world.<sup>10</sup> Major depressive disorder (MDD), is the most serious forms of depressive disorders, and also becoming a common chronic and recurrent psychiatric disorder.<sup>11</sup> MDD is characterized by impairments of social, occupational, educational, and cognitive functioning.<sup>12</sup> MDD is recognized as a growing global disease burden and one of the leading causes of morbidity, mortality, and economic burden.<sup>11</sup> Annually, 6% of adults suffer from MDD worldwide.<sup>13</sup> By 2010, MDD has become the second leading contributor to the global disability disease.<sup>14</sup> In addition, MDD will affect at least 350 million people by 2030, which expected to become the most leading cause of disability.<sup>15</sup>

Despite the existence of effective treatments, successful treatment, and response remain sub-optimal.<sup>16</sup> Over 20 years, adherence to medications in MDD has been an intractable clinical challenge.<sup>17</sup> Despite the high rate of medication nonadherence, there is a variation of adherence rate related to various methods used to measure medication adherence including self-reported, pill counts, pharmaceutical claims, biomarkers, physiological measures, and electronic medication monitoring.<sup>4,18</sup> Moreover, adherence to medication has been influenced by complex and multidimensional factors as barriers to reach successful treatment that includes patient-related, therapy-related, healthcare system, condition-related, and socioeconomic factors.<sup>3,19</sup> The literature has also identified a number of factors that may cause high rates of nonadherence to medication such as low education level, adverse side effects, uncertainty about treatment benefits, lack of education about medication, erroneous beliefs about the illness or medication, costs of medications, stigma, forgetfulness, lack of social support, and a negative relationship with the health care provider.<sup>21-25</sup> The complex situation and interferences between medical, psychological, environmental factors, as aforementioned, might be proposed as the underlying reason for medication adherence among patients diagnosed with MDD.

Nonadherent patients with MDD have a high risk of relapse and recurrence, rehospitalization, decreased reduction in the severity of depression, and growing suicidal ideation.<sup>16,25</sup> Although, previous literature has pointed out to optimize adherence to medication through designing and implement appropriate medication adherence enhancing interventions.<sup>22,26,27</sup> Indeed, different interventions help the enhancement of medication adherence,<sup>28,29</sup> include psychoeducation, motivational interviewing, psychosocial interventions, behavioral interventions, cognitive interventions, and cognitive-behavioral approaches.<sup>28,30-32</sup> Various health care providers have provided these interventions includes nurses, pharmacists, therapists, psychiatrists, and social workers.

Despite of high nonadherence and early discontinuation rates on patients with MDD, which earn attention toward these populations,<sup>33,34</sup> the literature on medication adherence among patients with psychiatric has focused on schizophrenia.<sup>35</sup> However, nonadherence contributes to unnecessary switches medication, unneeded changes in doses, initiation of unjustified adjuvant medications, and misdiagnoses of treatment-resistant.<sup>36</sup> So, it is crucial to attention to patients with MDD. Also, focus on the prevalence of adherence, factors affect to adherence, and interventions to improve adherence, which facilitates healthcare organizations, policymakers, and research organizations in the design and implementation of medication adherence enhancing strategies.<sup>37</sup> However, there is a need to expand the body of knowledge towards medication adherence in MDD.<sup>38</sup> Al-Jumah et al<sup>23</sup>, reported needing further studies to investigate the effect of interventions on factors that affect medication adherence. However, there is a scarcity and rising demand for scoping review, systematic review, and meta-analysis on the level of medication adherence, factors affect to medication adherence, methods to measure medication adherence, and medication adherence interventions among patients with MDD.

Major depressive disorder (MDD) can often be treated with psychological and pharmacological approaches.<sup>39,40</sup> Although international and national clinical practice guidelines recommend that the first line in MDD treatment is antidepressant (AD) medications, reducing the risk of relapse and recurrence by continuing AD medications from six months to five years after remission to prevent relapse and recurrence

is also a significant recommendation for good practice.<sup>40,41</sup> Expanding a better understanding of medication adherence prevalence, factors affect medication adherence, methods to measure medication adherence, and medication adherence interventions are of key importance to stakeholders, patients, healthcare providers, and policymakers. So, the purpose of this scoping review to highlight medication adherence prevalence, the factors affect medication adherence, methods measure medication adherence, and medication adherence interventions among patients diagnosed with MDD.

## Research Questions

The questions guided this review are: 1-What is the prevalence of medication adherence among patients diagnosed with MDD?

2-What are the most common methods used to assess medication adherence among patients diagnosed with MDD?

3-What are the factors that affect medication adherence among patients diagnosed with MDD?

4-What are interventions that have been implemented to enhance medication adherence among patients diagnosed with MDD?

## Method

### Protocol and Registration

The protocol of this scoping review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines.<sup>42</sup> The protocol of this study has been registered prospectively with the Open Science Framework on 21 November 2019 (<https://osf.io/a2jbr>). This methodology is a new approach used for several reasons, to examine the extent of emerging evidence, determine the value of researches, summarize and disseminate results, and identify the gaps in knowledge.<sup>43</sup> The scoping review involves the review, analysis, and synthesis of a broad scope of literature.<sup>42</sup> Also, it is offering an opportunity to clarify key concepts, research gaps, enhance practice, and evidence in policymaking and research.<sup>42,43</sup> The framework of this scoping review followed steps, identifying aims, identifying search strategies, determination of the inclusion and exclusion criteria for literature, data extraction, discussion of the findings, reconnoitering the limitations of the literature, and provide recommendation and implication from results for practice, policy, administration, education, and further research,<sup>42</sup> as presented in PRISMA-ScR checklist (supplementary-1). Congruently of purpose and questions, the current scoping review will report the variation of medication adherence rate, types of measurement methods, factors of nonadherence to medication, and types of medication adherence enhancing interventions.

### Search Strategy

The search strategy was developed by the principal author (A.K), in collaboration with the senior author (A.M), to identify relevant literature. The search of online electronic databases including, PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medical Literature Analysis and Retrieval System Online (Medline), and Cochrane Library was conducted as the sources of information for this review. The initial search was performed on Sep 20<sup>th</sup>, 2019, and the last search was on Nov 30<sup>th</sup>, 2019. These databases were selected to be comprehensive and cover a wide range of research papers. The search was conducted using the following keywords or search terms: Medication Adherence; Compliance; Patient Compliance; Adherence; Non-Adherence; Compliance; Non-Compliance; Antidepressant Agents; Antipsychotics Agents; Psychotropic Drugs; Drug Prescriptions; Drug Therapy; Major Depressive Disorder; Depression. Keyword combinations using Boolean operators (AND & OR), truncation, Medical Subject Headings (MeSH), and text-words (tw) were included in the search related to the purpose and research questions. All databases were interrogated using the same keywords or search terms in searches, which subjected to standardized procedures. The final search strategy for MEDLINE can be found in supplementary file 2.

### Inclusion and Exclusion Criteria

The authors (A.K and A.M) were involved in an iterative process to improve inclusion and exclusion criteria. The inclusion criteria of the selected articles in the current review were full text, published between the period of 2014 - 2019, English-language publications, involved human participants, and include studies of adult patients being treated for MDD as their primary diagnosis. The articles were relevant to major depressive disorder, medication adherence, and medication adherence enhancing interventions. Also, any type of quantitative, qualitative, and mixed methods studies included in order to consider different aspects of research designs. In addition, the articles were original research, a peer-reviewed study, or grey literature, and other relevant studies from the reference lists of the literature selected for review were included. Similarly, papers were excluded if did not meet inclusion criteria, the full-text article could not be retrieved, articles not available in the English language, did not contribute information on factors, prevalence, or interventions in medication adherence among MDD, and MDD related to secondary to traumatic brain injury, stroke, tumor, heart attack, or other non-psychiatric illness. Also, excluded letters, opinion statements, case reports, conference abstracts, editorials, commentaries, personal communications, and book chapters.

## Screening Process

Forms for the screening process were developed by principle author (A.K) and senior author (A.M) reviewed and validated it. The first level of screening, title and abstract of articles were independently screened for eligibility after deleting duplicate articles by two authors (A.K and A.M) using screening form, as outline in supplementary-3. After screening the titles and abstracts, two authors (A.K and A.M) independently screened full texts of articles for eligibility and assessed also using a standardized screening form, as outline in supplementary-4. The discrepancies on inclusion/exclusion of studies were resolved by discussion and consensus. Also, authors (A.K and A.M) was screened 30 articles by screening form to evaluate the agreement.

## Data Charting and Quality Assessment

Data were charted from each article independently by two authors (A.K and A.M) using a data charting sheet. This data charting sheet developed by principle author (A.K) and senior author (A.M) reviewed and validated it. The authors (A.K and A.M) was screened 15 articles by data charting sheet to evaluate the agreement and to ensure consistency with the research questions and purpose of the scoping review. Data charting was conducted using Microsoft Excel (Microsoft, Redmond, USA) spreadsheet and EndNote reference management software. The data gathered and charted from articles included articles characteristics (authors, year of publication, study location), study characteristics (the purpose of the study, study setting, number of participants, type of study, prevalence, factors, the method used to measure medication adherence, medication adherence enhancing interventions), and study findings (outcome variables, key findings). Any conflicts about data extracted were resolved by consensus.

The methodological quality of the included articles was assessed by two authors (A.K and A.M) independently. The authors used the Mixed Methods Appraisal Tool (MMAT)<sup>44</sup> to assess quantitative, qualitative, and mixed-methods studies, resolved disagreements by discussion and consensus. This MMAT checklist consists of two screening questions and five closed questions that are applied in all relevant studies. There are 25 criteria items to assess the quality of five different types of studies (qualitative research, randomized controlled trials, non-randomized studies, quantitative descriptive studies, and mixed methods studies); each type of study contains five criteria. The overall quality score can be checked with this tool for each study included. The tool results in a methodological rating of 0, 25, 50, 75, and 100 (with 100 being the highest quality) for each study based on the evaluation of study selection bias, study design, data collection methods, sample size, intervention integrity, and analysis.<sup>45</sup>

## Synthesis of Results

Data were collated and summarized in the form of text, tables, and figures. Initially, the data were summarized based on the general characteristics of the articles, such as the year of publication, study location, study setting. The results were summarized and described based on the purpose and research questions. Finally, the clinical, policy, administration, and research implications were described.

## Results

### Selection of Studies

The initial search of the online electronic databases yielded 1996 relevant articles, Pubmed  $n=638$ , MEDLINE  $n=363$ , CINAHL  $n=128$ , Cochrane  $n=851$ , and sixteen articles revealed from the reference lists (bibliographies) from the selected articles were examined and revised to identify additional relevant articles. After the removal of 624 duplicates article, 1372 remained, then screened the 1372 title and abstract, and excluded 1243 articles based on our screening form. One hundred twenty-nine full-text articles were reviewed and assessed for eligibility. Ninety-three additional articles were excluded for the following reasons: commentary & editorial ( $n=9$ ), not relevant outcomes ( $n=36$ ), not relevant study design ( $n=9$ ), other population (different psychiatric disorders and not involve MDD) ( $n=26$ ), MDD combined with other psychiatric disorders, and MDD developed from medical disease ( $n=5$ ), unobtainable ( $n=8$ ). A total of 36 articles were met the inclusion criteria for this scoping review. This selection process is shown in the PRISMA flow chart in Figure 1. As mentioned above, the result of the current scoping review was conducted congruent with four questions about the prevalence of medication adherence, methods used to assess medication adherence, the factors affect to medication adherence, and interventions to enhance medication adherence among patients diagnosed with MDD.

### Characteristics of The Included Studies

The general characteristics of the included articles are presented in Table 1. Of the 36 included articles that published between 2014 and 2019, eight articles were conducted in the United States, five articles were in India, and the other articles were conducted in Ethiopia, Saudi Arabia, France, Spain, Malaysia, Netherlands, Nigeria, Israel, China, Turkey, Nepal, South Africa, Australia, Iran, Thailand, Singapore, and Taiwan. Regarding the study designs, the majority of included articles (32) in this scoping review were quantitative study design, 23 of them were descriptive study (prospective, non-experimental, observational, retrospective cohort, Ex-post facto, cross-sectional study), and nine studies were experimental. Furthermore, three studies were qualitative study design, and one study was a mix method design. The sample size was 42,586 patients were included in this scoping review, ranging from 18 to 14,135 patients. The age varying between 18 and 88 years, and the majority of the sample was female. Twenty-nine studies recruited samples from the outpatient setting.

### Methodological Quality of Included Studies

The Mixed Methods Appraisal Tool (MMAT)<sup>44</sup> used to assess included quantitative, qualitative, and mixed-methods studies. There was a meaningful variation in the methodological quality of the included articles, with scores ranging from 25% to 100%; the score of each type of study is judged within its methodological scope as presented in Table 2. Also, the distribution of study design with study quality is presented in Table 3. The majority of studies ( $n=18$ , 50%) were methodologically adequate ( $>75\%$ ), noting that design and research perform were generally appropriate. Thirteen studies (36.1%) in score 75%, four studies (11.1%) in score 50%, and one study (2.8%) in score 25%.

### Prevalence of Medication Adherence in Patients With MDD

The included articles investigated medication adherence to AD medications or concomitant with antipsychotics, anxiolytics, mood stabilizers, and psychostimulants medications. Although thirty-three included studies used adherence measurement methods, ten of them not measure the prevalence, which five included studies not mentioned the medication adherence level, and five included studies examined intervention. Although, the prevalence of medication adherence among patients diagnosed with MDD was found to range from 10.6% to 85.4%, as presented in Table 4, this variation depends on the data collection method used to measure medication adherence and the period of measure.

### Methods to Assess Medication Adherence

The descriptions of data collection methods are presented in Table 4. Out of 33 studies used data collection

methods to measure medication adherence, 22 (66.6%) studies used a self-report data collection method, pharmacy refill and claims database 9 (27.3%), and pill count 2 (6.1%). Moreover, the selected studies used various data sources; the majority obtained from patients (n=21), and direct methods were not used in the included studies. As previously mentioned the variation of the prevalence of medication adherence, the rate of adherence as assessed by using self-reported, claims database/refill data, pill count, health provider's report (self-report, patient record) ranged from 10.6% to 81%,<sup>19,21-23,34,46-62</sup> 10% to 62.9%,<sup>25,34,63-70</sup> 45%,<sup>71,72</sup> and 69.2% to 85.4%,<sup>34,58</sup> respectively. The most common included studies utilized standardized and structured data collection tool, and structured interviews to measure adherence. Morisky Medication Adherence Scale-8 items (MMAS) and the four-item Morisky Green Levine Medication Adherence Scale (MGLS) self-report measure was the most common measures used for evaluating medication adherence, which was applied in 5 (23.8%),<sup>22,23,46,47,51</sup> and 4 (19%) studies,<sup>52,53,55,56</sup> respectively.

Nine studies used the electronic data records (pharmacy or medical claims database) to measure medication adherence, which different measures were utilized, including the percentage of days covered (PDC), medicine possession ratio (MPR), prescription fill, and missing days. The PDC is the number of days a patient gets each medication divided by the number of days for eligibility for medication, greater than 80% mean patient have adequate adherence, which 80 % considered cut-off between adherent and nonadherent patients as used by LeBlanc et al.<sup>68</sup> Also, the MPR is the number of days that doses were dispersed divided by the total number of days between the first and last doses. It is dichotomized into greater than 80% considered adherent and lower than or equal 80% considered nonadherent as used by Holvast et al<sup>66</sup>, and Slabbert et al<sup>69</sup> reported that patients considered adherence if MPR was between [?]80% and [?]110%.

Regarding prescription fill and missing days, nonadherence described if medication discontinued before 180 days after the index refill date.<sup>63</sup> Other studies defined adherence as the proportion of compliance during the first 24 weeks from prescription fill.<sup>67</sup> Also, Yau et al<sup>25</sup> measured adherence as filled prescriptions for medications with no gaps of more than 15 days within six months after the start of treatment. On the other hand, two studies used pill count by calculating the actual number of pills taken dividing by the expected number of pills taken during the study period and multiplying by 100.<sup>71</sup> Other study was calculated by the total number of weeks the participants took medication.<sup>72</sup>

## Factors Affect to Medication Adherence

Several factors have been shown that hinder patients from taking their medication as prescribed. World Health Organization (WHO) has categorized common factors that affect adherence to five different dimensions.<sup>3</sup> The five dimensions of adherence are socioeconomic, healthcare provider/system, illness, medication, and patient-related factors.<sup>3</sup> As described below, these five dimensions used in this scoping review to extract the factors from included studies. Factors that could contribute to medication adherence among patients diagnosed with MDD are summarized and presented in Table 5. However, studies are not consistent about the relationship between factors and adherence. Over 33 included studies, 26 of them investigated the factors that influence medication adherence. The following section will explore commonly reported reasons and factors associated with adherence to medications.

**Socioeconomic related factors.** Language and literacy have been associated with the adherence level.<sup>64</sup> By using different self-reported assessment methods, medication adherence was related significantly to income,<sup>56,57</sup> level of education.<sup>52,57</sup> Regarding living conditions, Yau et al<sup>25</sup> noted that the type of accommodation associated with noncontinuous use of AD medications. Patients whose accommodation in public housing property that reflects low socioeconomic status was related to noncontinuous use of AD medications.<sup>25</sup> On the other hand, the occupation of patients has a relationship with an adherence level of medication. Also, patient occupation in service and farming reported a significantly high adherence rate than business, housewife, and students.<sup>60</sup>

Lack of family support and the nature of the job stated the reasons for nonadherence.<sup>57,65</sup> Studies conducted in different contexts reported that lack of support from family members, spouses, and friends was found barriers from delayed initiating AD medication and continuing it.<sup>24,73</sup> Also, Ho et al<sup>24</sup> and Vargas et al<sup>74</sup>

noted that social-cultural stigma influences on adherence, which stigmatizing views held by others in patients' social circle were depression is a sign of madness and negative personal characteristics. Moreover, religion and cultural beliefs have been barriers to medication adherence.<sup>24</sup>

**Healthcare provider/System-related factors.** Accessibility to healthcare services included long-distance, poor access to healthcare locations, long waiting time at the clinic, limited time with psychiatric doctor, and lack of accessible appropriate material influence to medication adherence. Compared to the short distance, patients who move to the psychiatric clinic from long-distance five times nonadherent to medications.<sup>22</sup> Ho et al<sup>24</sup> reported that patients who have experienced long waiting times at the clinic and lack of transportation to healthcare locations hospital resulted in patients not taking medications. Also, poor of access to different formats of informational materials in psychiatric clinic influence on medication adherence, which included lack of verbal and written instructions and information, use different language in instructions and information, and use appropriate format for patient with physical disability (e.g., hearing and visual impairment).<sup>64</sup> Furthermore, the limited time of follow-up visits with the psychiatrist in the clinic affects adherence to medication.<sup>64</sup>

The change of psychiatrists and multiple prescribers every visit affects the patient's confidence and trust toward providers, which later affected their medication-taking behavior,<sup>24</sup> and non-availability of psychiatrists during follow-up one of the reasons for nonadherence.<sup>57</sup> In addition, the satisfaction level of the patient with psychiatrists is related to adherence.<sup>21</sup> On the other hand, the frequency of follow-up visits to psychiatric clinic affects adherence to medications.<sup>21,24,34</sup> The lower number of visits to clinics related significantly to a low level of adherence to AD medications.<sup>23,25</sup>

Ho et al<sup>24</sup> presented the poor communication between the patient and provider could impede medication adherence. In addition, inadequate information on medications and disorders, and healthcare provider guidance related to the low level of adherence (Srimongkon et al. 2018).<sup>57,64</sup> In spite of appropriate information and guidance, access to medication in facilities are still relating to continuous taking medications.<sup>24,57,73</sup>

**Illness-related factors.** Acute onset of the illness associated with the early withdrawal was experienced in the patients with MDD.<sup>65</sup> Also, earlier MDD diagnostics minimize the non-continuous behaviors of AD medication.<sup>25</sup> For the duration of illness, a short duration of illness significant in relation to high rates of adherence.<sup>23</sup> Alekhya et al<sup>21</sup> noted the correlation between low adherent patients with patients experienced more than a year of illness. In the same way, the risk of nonadherence to medication in patients who have been diagnosed MDD for more than two years is high.<sup>22</sup> Furthermore, the adherence to medication is influenced by symptoms and the severity of the disease. Lucca et al<sup>57</sup> demonstrated that patients reported forgetfulness, no improvement, and deterioration of conditions impaired the adherence to medication. A phenomenological study reveals that depressive symptoms; forgetfulness, lethargy, and laziness impair the adherence of AD medications.<sup>73</sup> Similarly, other studies have shown that somatic symptoms associated with an early dropout of treatment.<sup>65</sup> Furthermore, nonadherent patients are closely associated with high physical pain.<sup>48</sup> De las Cuevas et al<sup>52</sup> have found that patients with a severe degree of depression related to nonadherent patients. However, the opposite association between adherence and depression severity, which clarified that lower depressiveness was significantly correlated with higher medication adherence rates.<sup>23,48</sup> In another study, the research in Beijing has revealed that few episodes of preceding depression had a significant impact on medication adherence that had a positive relationship to increased medication adherence.<sup>56</sup> The number of psychiatric hospitalizations influence factors to medication adherence. A more significant number of psychiatric hospitalizations correlated with a high degree of non-compliance medications have been reported by Baeza-Velasco et al.<sup>48</sup> In addition, in co-morbid illnesses, included studies have reported that patients with MDD who comorbid with physical illnesses, alcohol dependence and illicit drug, and concomitant psychiatric illness negatively interfered with adherence to AD medications.<sup>21,22,24,65,48</sup>

Conversely, patients with co-morbid anxiety exhibited high adherence to medications.<sup>56</sup> Patients with a family history of depression and past history of depression were also strongly in nonadherence.<sup>21</sup> Also, in patients with a suicidal ideation and attempts, a poor adherence level is also substantially increased.<sup>21,48</sup> Indeed, a cross-sectional study was performed of patients with bipolar disorder, schizophrenia, schizoaffective,

depression, and other psychiatric disorders at the psychiatric clinic, which showed that the diagnosis had a major effect on nonadherence to medications.<sup>34</sup>

**Medication-related factors.** According to recent studies, complex treatment regimens impair adherence significantly. Alekhya and colleagues<sup>21</sup> found out that polypharmacy has a major impact on adherence; the most significant number patients are not adhering to a multiple drug system. Also, patients with co-morbidities discontinue AD medications related to the barrier of pill burden, which they are taking so many types of medications.<sup>24</sup> In addition, statistically significant is the relationship between the number of prescription medications and medication adherence.<sup>49,57</sup> Moreover, previous studies stated that adverse reactions have association with level of medication adherence.<sup>21,25,49,62,64,65,73</sup> In addition, nonadherence is related to severity and the amount of adverse effects.<sup>52</sup> Ho et al<sup>24</sup> reported that patients have stopped taking medications associated with the experience of side effects. Other included studies have found that patients with MDD describe and stated that the majority of reasons for nonadherence are an adverse reaction.<sup>34,57,60</sup>

The duration of treatment can also affect adherence to medications. Findings by using MPR reported that statistically and practically important the duration of treatment is correlated with adherence to medication.<sup>69</sup> Lucca et al<sup>57</sup> noted that during the first three months of treatment patients continue to take medication with a significant association with medication nonadherence. The qualitative study concluded that patients who are concerned about the long-term effects of AD medications have a negative effect on the implementation of therapy.<sup>73</sup> Inconvenient dose regimen may affect medication adherence, which explained that doses could be needed once a day, twice a day, three times a day or more than four times a day.<sup>73</sup> In other studies, the cost of medication was a factor for nonadherence,<sup>57</sup> and is correlated substantially with nonadherence.<sup>60</sup> Studies that have assessed adherence to the prescribed class of medication reported that the type of active ingredients consumed or formulations and adherence were significantly related.<sup>57,69</sup> However, the most common reason for discontinuance was the ineffective response of the medication.<sup>58</sup>

**Patient-related factors.** Patient factors associated with medications adherence represent sociodemographic factors (age, gender, race, marital status), psychological factors (beliefs, attitudes, satisfaction, knowledge, psychological reactance, locus of control, self-stigma, self-motivation, insight, self-management), and physical (cognitive and behavioral) factors (forgetfulness, the patient's personal obligation, carelessness, confusion).

Age considered the predictor of adherence to prescribed medications, in Spain, adherence to AD medication was assessed in the two community mental health centers located on Tenerife Island, and the result was that the likelihood of adherence to the medication for older patients was lower.<sup>53</sup> A study that has compared the level of adherence reported lower adherence levels for patients older than 60 years than for patients aged 18-40 years.<sup>69</sup> In contrast, Al-Jumah et al<sup>23</sup>, found that older patients had a high level of adherence. In addition, young age patients significantly associated with noncontinuous use of AD medication.<sup>25</sup>

Gender is an important factor in the non-continuing use of AD medications, with female patients showing a high level of non-continuous use of AD medications.<sup>25</sup> In addition, the energetic disparity of the male is a statistically important differentiation for adherence.<sup>23</sup> However, race-gender also associations with adherence, AD adherence difference across four race-gender subgroups (African-American women, African-American men, White women, and White men), white women more likely to be adherent to their AD medication 3.1 times than African-American women.<sup>50</sup> Moreover, marital status exhibits significant differences in the level of medication adherence. According to Baeza-Velasco et al<sup>48</sup> reported that high adherent patients have a partner.

A patient's beliefs are influence decisions of medication-taking behavior, the necessity beliefs of medications associate positively with adherence to medication; likewise, the beliefs of concern, harmfulness, and overuse related with nonadherence to medication.<sup>23,49,51,62</sup> The beliefs that psychiatric medications general harmfulness is in relation to nonadherent patients.<sup>52</sup> Nonadherent patients displayed a high degree of concern for medications perceived to have potential adverse effects, such as dependence, side-effects, or accumulation effects.<sup>52</sup> In another study, the belief that the medication relieves the symptoms, does not relieve the symp-



toms, increases the severity of the disease, and the belief that they do not suffer from a psychiatric illness; these reasons impressed continuous of treatment.<sup>65</sup> In addition, patients have reported necessity beliefs such as AD that help treat depression, safe for most patients; it must be taken daily for several weeks to ensure it works, which positively affects their adherence.<sup>64</sup> Also, harm beliefs that explained that medications are addictive associated with a low level of adherence.<sup>64</sup> Other study presented that patients showed incorrect beliefs about MDD and AD medications, and harm beliefs of fear of medication dependence that related to adherence.<sup>24</sup>

Indeed, high necessity beliefs significant predictors of high AD medication adherence which explained through patients' beliefs that AD medication could protect against exacerbation of depression; without AD medication, they will be very depressed; the mental health status will depend on AD medication.<sup>56</sup> Also, negative impact between the concern beliefs about the AD medications and AD medication adherence expressed through concern about their long-term consequences, heavily depends on them, they are a mystery, they disturb life.<sup>56</sup> Srimongkon et al<sup>73</sup> reported that the patients' beliefs that medication efficacy has a positive influence on adherence and negative factors on adherence in patients with concern regarding therapeutic effects and side effects of medications. Qualitative interviews of the experiences of Latino outpatients with MDD investigated depression and pharmacotherapy perspectives, concluded that patients had concerns regarding medications and depression that may have been perceived as obstacles to treatment and medication adherence.<sup>74</sup>

Concern beliefs over the fear of dependence on AD medications, physical ramifications for taking AD medications, risk of deteriorating depression and mental health, high dosages of prescription are hazardous, irrepressible adverse effects, and alternative cures have less antagonistic impacts than AD medications.<sup>74</sup> Also, concern beliefs about depression referred that depression is exacerbated and not relive.<sup>74</sup> Other barriers are beliefs about AD medications use that disagreement with psychiatric advice, which patients believe that it is the last choice, it is should work immediately, it is used when feeling depressed and take high doses of it, and not take when feeling better.<sup>74</sup> In addition, the fear about the medications and from addiction are barriers to medication adherence.<sup>57,74</sup>

On the attitude towards medication, there is a positive attitude related to adherent patients,<sup>48,52,64</sup> and vice versa.<sup>24</sup> According to statistical differences between adherent and nonadherent patients, adherent patients show a stronger positive attitude than nonadherent patients.<sup>59</sup> In addition, low-level adherence to AD medication is associated with low treatment satisfaction<sup>23</sup>, lack of knowledge.<sup>24</sup> On the other hand, adherence to medications can be influenced by a negative emotional reaction to regulations or recommendations of medication use that affect freedom and autonomy, and beliefs regarding the control of health. Psychological reactance and chance external locus of control have positive associations and levels of adherence, where more reactant patients are less adherent, also a negative relationship with an external locus of control, where more adherence when patients depend on their doctors.<sup>53</sup>

Patients who take AD medications seen is a sign of not normal and effect on behavior and mental state, so this self-stigma towards AD medications affect medication adherence.<sup>74</sup> Also, self-stigma over depression, denial about their disorder, nonacceptance of the disorder considered the major reason for noncontinuous AD medication.<sup>25,34,73</sup> On the other hand, the expression of patients that want to feel better and experience severe depressive symptoms that motivate adherence to AD medications. Srimongkon et al<sup>73</sup> reported that patients revealed that self-motivation and self-management have a positive impact on adherence. Although, the insight of diagnosis may factor that influence adherence.<sup>24,57</sup> Moreover, patients revealed that forgetfulness is a negative effect on medication adherence.<sup>24,60</sup> The patient's personal obligations such as traveling; carelessness; and confusion negatively influence AD medication adherence.<sup>57,60</sup>

## Interventions Strategies for Improving Medication Adherence

Ten of the 36 included studies have evaluated the effectiveness of various interventions to improve medication adherence among patients diagnosed with MDD as presented in Table 6. Since adherence was related to health outcomes, medication adherence enhancing interventions should design and implement that can

reflect in increase the number of patients who adhere to medication. These have ranged from single element interventions and through to multi-element intervention packages. These interventions have been categorized into counseling (cognitive, behavioral interventions), education and information, reminders, monitor feedback (adherence and disease), and multi-faceted intervention. Multi-faceted interventions defined as intervention including two or more components such as education with monitor feedback, and cognitive education with counselling.<sup>75</sup> Out of 10 studies, five randomized controlled studies, one cluster randomized trial study, one randomized controlled trial with two parallel-group posttest-only study, one pre-post one-group intervention study, one observational retrospective cohort study, and one prospective nonrandomized open-label naturalistic observational study.

In two studies the intervention was delivered as integrated service in primary health centers by pharmacists and pharmacy students to examine intervention,<sup>49,67</sup> other study was delivered enhanced care home visits in primary health centers after the first medical consultation by community health workers.<sup>72</sup> Hammonds et al<sup>71</sup> used electronic medication reminder application through a smartphone device to enhance adherence to AD medications and evaluated after about 35 days from the initial assessment. Also, bibliotherapy and text messaging a novel approach delivered as counseling (cognitive, behavioral interventions) developed by psychologists, psychiatrists, and community medicine specialists.<sup>61</sup> Five studies were provided the intervention from 1 to 4 sessions to patients by pharmacists, psychiatrist, physicians, social workers, nurses, and candidate master degree researcher.<sup>19,47,54,62,68</sup>

**Interventions Based on Monitored Adherence Feedback.** The use of pharmacy management service and community healthcare service has been shown to have positive effects on medication adherence.<sup>49,67</sup> Pharmacist-led multidisciplinary AD telemonitoring service provided monitoring of patients for early interventions following AD initiation or up-titration to enhance adherence, relieve adverse effects, and minimize suicide risks through education and information and monitor feedback (adherence and disease).<sup>49</sup> Also, community pharmacists (CPs) management which used education and information, reminders, and monitor feedback (adherence and disease) approach, compared CP management with treatment-as-usual (TAU) after 1 and 6-months AD treatment adherence rate was high among patients received CP management.<sup>67</sup> Other study was delivered enhanced care home visits as education and information and monitor feedback (adherence and disease) in primary health centers after the first medical consultation by community health workers. The enhanced care home visits group as a treatment intervention (TI) showed a significant completed the treatment and treatment adherence compared with the treatment as usual (TAU) group. However, there was no significant difference in the outcomes of depression at six months follow up.<sup>72</sup>

**Interventions Based on Reminder Systems.** Use of electronic medication reminder application increase adherence to AD medications.<sup>71</sup> Electronic medication reminder application via smartphone for about 35 days in a randomized, parallel-group clinical trial enhance adherence to AD medications in college students.<sup>71</sup>

**Education and Information Interventions.** The use of information in a different form of delivery, verbal, written, or audiovisual. These interventions are designed to educate patients to promote medication adherence and motivate patients by sufficiently describing the way of taking medication, producing and discussing with patients any reluctance to take medication, and discussing with patients their beliefs and knowledge about their condition and treatments.<sup>47,68</sup> This intervention focuses on patients, context, and health care system, which adopting patient-centered care and sharing decision-making principles.<sup>47,68</sup> Providing information about AD medications by pharmacist interventions, it significantly improves medication adherence, treatment satisfaction, general overuse beliefs, and specific concern beliefs. However, the severity of depression and health-related quality of life did not make a difference between the interventional and control group after six months.<sup>47</sup> However, other studies used depression medication choice as a novel shared decision-making approach, compared with usual care found that no difference in medication adherence, depression control, or encounter duration.<sup>68</sup>

**Cognitive-Behavioral Counseling Interventions.** Cognitive-behavioral therapy (CBT), as a new discovery, which is being applied in the field of psychotherapy, has proven effective in improvements in self-concept, pessimistic worldview, negative thoughts, and medication adherence.<sup>32</sup> The use of a novel approach

of cognitive-behavioral interventions through bibliotherapy (booklet) and text messaging by allocated to three groups, control, booklet, and booklet and text messaging. The data collected three times: before the intervention, immediately after intervention, and three months after intervention. Medication adherence insignificant within each group at different times, while it was statistically significant in the interactive effect of group factor and the time factor.<sup>61</sup>

**Multi-Faceted Intervention.** A single element approach has limited effectiveness on medication adherence because the factors determining adherence interact and potentiate each other's influence.<sup>3,32</sup> On the other hand, adequate evidence has been supporting that multi-faceted most effective approach, which targets more than one factor by more than one strategy. Several programmers have demonstrated effective outcomes using a multi-elements approach.<sup>19,54,62</sup> Examples include the treatment initiation and participation program (TIP), drug adherence enhancement program, and psychoeducation with basic CBT strategies.<sup>19,54,62</sup> Particularly, multi-elements approach significantly improvements in the knowledge of depression, attitude towards medication adherence, and reductions in depressive symptoms compared with TAU.<sup>19,54,62</sup>

Furthermore, the use of pharmacy management service and community healthcare service as a multi-faceted approach has been shown to have positive effects on medication adherence.<sup>49,67,72</sup> Pharmacist-led multidisciplinary AD telemonitoring service provided monitoring of patients for early interventions following AD initiation or up-titration to enhance adherence, relieve adverse effects, and minimize suicide risks through education and information and monitor feedback (adherence and disease).<sup>49</sup> Also, community pharmacists (CPs) management which used education and information, reminders, and monitor feedback (adherence and disease) approach, compared CP management with treatment-as-usual (TAU) after 1- and 6-months AD treatment adherence rate was high among patients received CP management.<sup>67</sup> Other study was delivered enhanced care home visits as education and information and monitor feedback (adherence and disease) in primary health centers after the first medical consultation by community health workers. The enhanced care home visits group as a treatment intervention (TI) showed a significant completed the treatment and treatment adherence compared with the treatment as usual (TAU) group. However, there was no significant difference in the outcomes of depression at six months follow up.<sup>72</sup>

## Discussion

As described at the beginning in this scoping review, medication nonadherence is a problem affects the health care system, healthcare professionals, and patients. So, to the best of our knowledge, this is the first scoping review that summarize and identify medication adherence rate, types of measurement methods, factors of nonadherence to medication, and types of medication adherence enhancing interventions among patients with MDD. Our findings provided many insights into the importance to focus on the prevalence of adherence, factors affect to adherence, and interventions to improve adherence in patients with MDD. Also, attention and expand the body of knowledge towards medication adherence in MDD facilitates healthcare organizations, policymakers, professions, and researcher in the design and implementation of medication adherence enhancing strategies.

This scoping review included 36 in the past 5 years met our eligibility criteria, selected by using selection process of PRISMA-ScR guidelines.<sup>42</sup> The authors attempted to adjust the need to lessen the heterogeneity of selected studies for the one hand while assuring the fitting impression of valid practice on the other. Consequently, the main results divided according to the research questions. In the identified articles, the current authors noted that the quality of the most included studies was generally good, except for one study by Shrestha Manandhar et al<sup>60</sup> which yielded the lowest score (25%) using MMAT. The authors identified the prevalence of medication adherence are range from 10.6% to 85.4%, and the rate of medication adherence in majority of studies are low (<60%).<sup>21-23,25,46,48,52,53,55,56-58,60,63-71</sup>

Concerning the variation of adherence rate, the current authors were unable to standardize the adherence rates related to the variation in study designs, adherence measures, and inconsistent definitions of medication adherence were associated with unacceptable heterogeneity. Regarding the adherence measures, researchers used various methods in an attempt to assess patient adherence to medication, but none of them can be

considered universally accepted "gold Standard" for measuring adherence. The majority of studies in this scoping review used indirect measures such as self-reported questionnaires and pharmacy refill data. This is because direct methods such as biological measures are not always acceptable, appropriate, feasible, or cost-effective.<sup>18</sup> This view potentially explains that most studies (22) measuring adherence based on self-report as subjective measurements, there were 12 different measures. Also, nine studies used objective measurements by using the electronic data records and two studies used pill count. Although, views as to the best measurements vary, each is acknowledged to have its advantages and limitations. The advantages of indirect measures in these studies are flexible, easy to administer, relative unobtrusiveness, inexpensive, and time-saving to complete. However, limitations may be subject to bias (e.g., refill prescription is different to ingestion of medication), social desirability, and overestimate adherence.<sup>19,25,47,53-55,57,58,69,70,72</sup>

However, 26 of included studies investigated the factors that influence medication adherence among patients with MDD. This scoping review identifies multi-factorial causes leading to poor medication adherence, which classified as WHO into five categories: socioeconomic, healthcare provider/system, illness, medication, and patient-related factors.<sup>3</sup> This scoping review recognizes illness, medication, and patient-related factors were the most factors associated with medication adherence. This explained that the common factors to adherence are under the patient's control, which patient's perspective toward illness and medication maybe is a considered decision by patients making their own choices about taking medications, based on their beliefs, personal conditions, and the information offered to them.

However, various interventions address the aforementioned factors to improve adherence. With an understanding of the factors that influence medication adherence among patients with MDD, proper intervention can then be tailored individually to improve the medication-taking behavior of each patient. Our scoping review identified ten studies that used a range of counseling, education and information, reminders, monitor feedback, and multi-faceted intervention to improve medication adherence among patients with MDD. These interventions implemented by many different health care workers who have an essential role in improving adherence because they can influence one or more of the factors that determine adherence.

The number of studies with either positive or no effects. The most common interventions targeting healthcare provider/system and patient-related factors were evident such as Aljumah & Hassali<sup>47</sup>, Isa et al<sup>54</sup>, Sirey et al<sup>19</sup>, Taleban et al<sup>61</sup>, and Vannachavee et al<sup>62</sup>. The present review showed that a single-element intervention might be expected to have been less effective on medication adherence.<sup>47,61,68,71</sup> However, there is no universal intervention that is suitable for all nonadherent patients. In this scoping review, multi-faceted intervention is most interventions used in 6 included studies. In addition, the six studies presented a significant result about improving medication adherence. Nieuwlaat et al<sup>32</sup> noted that effective intervention is complex, involves several components to address a multi-factorial approach that effect on medication adherence.

However, healthcare professionals play an essential role in assessing patients with nonadherence and delivering appropriate interventions to support and improve adherence, persistence, and retention in medication and care. Also, nurses play a key role in screening, assessing, and promoting medication adherence.

## Limitations

The following limitations should be mentioned for this study. First, the search was limited to the last five years and English language publications. Second, this is not a comprehensive review of all the existent medication adherence measures and interventions. However, it focused on the different types available and the most commonly used among patients with MDD.

## Conclusion

The results of this scoping review highlight that nonadherence to the medication among patients with MDD is a major obstacle in reducing public health challenges in both developed and developing countries. The evidence shows that patients with MDD have a high rate of medication nonadherence. However, accurate assessments of medication adherence will provide better evidence on the outcomes, risk factors, and interventions to improve medication adherence. Numerous measurements available for assessments of

medication adherence, also need to prove to be valid, reliable, and sensitive. However, the selection of measurements should be based on researcher or healthcare professionals' attributes, goals, resources of the clinical setting, or study. Although, none of the measurements can be considered as a gold standard, and the triangulation of measures is recommended. The behaviors of taking medication are often faced multi-factorial causes, identify of it important to implement appropriate medication adherence enhancing interventions. Also, interventions require several components to focus on these factors, and health care professionals must follow a systematic process to assess possible factors.

## Implication

The findings of this scoping review presented important implications for practice, administration, policy, education, and future research. For practice, healthcare professionals need to integrate assessments of level, reasons, and factors that influence medication nonadherence into practice. They need to improving medication adherence and understanding factors that influence nonadherence behavior can enable healthcare professionals to identify interventions and improve the patient's adherence behaviors and long-term health outcomes. Moreover, they should aim to maintain medication adherence through involvement healthcare professionals in providing medication adherence enhancing interventions to improve patients' beliefs and behaviors, as well as use multi-faceted intervention and ongoing follow-up, which may assist patients in achieving greater long-term adherence to medication. Although should providing training for healthcare professionals on assessments of level, factors that influence medication nonadherence, communication skills, and provide continuous monitoring for patients. In addition, this scoping review confirms to formalization and integration of the adherence assessment process into routine practice and highlights the importance of multidisciplinary support required for a successful assessment of medication-taking behavior.

For administration, this could be achieved by integrating and designing appropriate assessment measures and interventions regarding MDD and medication adherence. For policy, it should emphasize a collaborative effort of researchers, healthcare professionals, and stakeholders to improve medication adherence. Also, emphasize integrate statistics of medication adherence into the healthcare databases. This highlights to focus on and increase the number of medication adherence enhancing interventions that are supported by health care institutions. Also, develop a guideline for medication adherence measures, medication adherence enhancing interventions, and follow-up strategies.

For education, nursing students should be aware of the concept of adherence, the outcome of nonadherence, and the interventions of adherence. Particularly, measures, influencing factors, and types of medication adherence enhancing interventions should be taught in nursing programs. In addition, health nursing care plans may need to include medication adherence and self-monitoring assessment to be standard for students clinical practice. Therefore, nursing programs should focus on teaching students how to assess medication adherence.

The current scoping review could be extended and improved upon in several areas. For future research, we need research on nonadherence to medication among patients with MDD as well as interventions to promote patients' adherence to treatment, as most of the research that was identified was recommended only in specific settings, diseases, treatments, and it included small samples of the study. The researchers could utilize rigorous methodological approaches and focus on investigating clinical features and factors that could influence medication adherence among patients with MDD. In addition, the researchers could utilize objective measures of adherence, and triangulation of methods is recommended that could give more naturalistic and precise findings. Future research can also explore and develop additional and new interventions to address factors that could influence medication adherence as well as the effectiveness of current efforts to enhancement adherence to medication among patients with MDD.

## Authorship

The authors participated in the process of systematic retrieval, evaluation, analysis of studies, results, and manuscript preparation; details of each contribution are presented in the method section. Results and manuscript preparation.

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**Table 1** . Characteristics of Selected Studies (n = 36)

Author (year)	Country	Study design	Study setting	Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))	Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))	Purpose of study	Outcome variables
Sirey et al. (2017) <sup>19</sup>	USA	Quantitative (Random- ized clinical ef- fectiveness trial)	Outpatient	n=sample size 231	I:C (115, 116)	The purpose to test the ef- fectiveness of TIP to improve early adherence among older patients whose primary care physician newly initiated an antide- pressant for depression.	Medication adherence and depression severity
Alekhyia et al. (2015) <sup>21</sup>	India	Quantitative (Cross sectional study)	Outpatient	103		Study the treatment and disease factors that influence compli- ance to the treatment of depression.	Medication adherence; and disease and treatment factors

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Abegaz et al. (2017) <sup>22</sup>	Ethiopia	Quantitative (Prospective cross-sectional study)	Inpatient and outpatient	270		The purpose to determine the degree of adverse drug reactions of antidepressants and their impact on the level of adherence and clinical outcome.	Adverse drug reactions, medication adherence, and clinical outcomes (depression)
Al-Jumah et al. (2014) <sup>23</sup>	Saudi Arabia	Quantitative (Non-experimental cross-sectional design)	Outpatient	403		The purpose to explore patients' adherence to antidepressant medication, and the factors associated with adherence among patients with depression.	Medication adherence and beliefs about medication

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Ho et al. (2017) <sup>24</sup>	Malaysia	Qualitative (Grounded theory methodology)	Outpatient	30		The purpose to explore the barriers and facilitators of patients' adherence to antide- pressants among outpa- tients with MDD.	Barriers and facilitators of medica- tion adherence
Yau et al. (2014) <sup>25</sup>	China	Quantitative (Retro- spective cohort study)	Outpatient	189		The purpose to investigate the rate of noncontin- uous antide- pressant use, subse- quent rate of relapse and recurrence in psychi- atric Chinese outpa- tients, and factors associated with non- continuous antide- pressant use.	noncontinuous antide- pressant use, factors associated with non- continuous antide- pressant, and subse- quent depression relapse and recurrence

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Mert et al. (2015) <sup>34</sup>	Turkey	Quantitative (Cross- sectional study)	Inpatient	203 (n=39 patients with depression)		The purpose to evaluate factors resulting in medica- tion nonadher- ence before admission to the psy- chiatric service for patients with psy- chiatric disorder.	Socio- demographic and clinical variables, medica- tion adherence, and reasons of medica- tion nonadherence
Al-Jumah et al. (2014) <sup>46</sup>	Saudi Arabia	Quantitative (Non- experimental, observa- tional design)	Outpatient	403		The purpose to investigate the rela- tionship between patient treatment satisfac- tion and adherence to antide- pressants, and the role of patient beliefs toward medica- tion in patient treatment satisfaction.	Medication adherence, treatment satisfac- tion, and beliefs about medication

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Aljumah and Hassali (2015) <sup>47</sup>	Saudi Arabia	Quantitative (Prospec- tive random- ized controlled study)	Outpatient	239	(119, 120)	The purpose to assess whether pharma- cist interven- tions based on SDM improved adherence and patient- related outcomes.	Medication adherence, beliefs about medica- tion, clinical outcomes (depres- sion symp- toms), patient in- volvement in decision- making, quality of life, and treatment satisfaction

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Baeza- Velasco et al. (2019) <sup>48</sup>	France	Quantitative (Cross- sectional study)	Inpatient and outpatient	360		The purpose to explore medica- tion adherence in patients with a major depression episode, and to identify sociode- mo- graphic, clinical, and psy- chosocial factors related to adherence status.	Medication adherence, clinical and psy- chosocial factors (depres- sive symp- toms, psychi- atric an- tecedents, comorbid- ities, medica- tion, pain, medica- tion side effects, negative life events, childhood trauma, and attitudes to medication)

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Bhat et al. (2018) <sup>49</sup>	USA	Quantitative (Observa- tional retrospec- tive cohort study)	Outpatient	258		The purpose to evaluate the feasibility of imple- menting a clinical pharma- cist led multidisci- plinary antide- pressant telemoni- toring service, evaluate potential opportuni- ties for clinical pharmacy interven- tion, and identify which patients with major depressive disorder would be most likely to benefit from this service in primary care.	Medication adherence, adverse effects, suicidal ideations, depressive symp- toms, and pharma- cist interventions.



<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Burnett- Zeigler et al. (2014) <sup>50</sup>	USA	Quantitative (Prospec- tive, observa- tional study)	Outpatient	186		The purpose to examine the associ- ations between treatment attitudes and beliefs with race- gender differences in antide- pressant adherence.	Medication adherence, demo- graphic variables, illness variables (past antide- pressant use, number of prescribed medica- tions, physical health status, mental health status, comorbid anxiety, somatic anxiety, and de- pression), activities of daily living and executive function, attitudes and beliefs toward depression treatment, and stigma

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Chatterjee et al. (2017) <sup>51</sup>	India	Quantitative (Ex-post facto design (criterion- group design))	Outpatient	60		The purpose to explore belief about the medica- tion influences adherence to medica- tion, and influence severity of depression and quality of life of patients with MDD residing at urban and rural areas.	Medication adherence, beliefs about medica- tion, depressive symp- toms, and quality of life

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
De las Cuevas et al. (2014) <sup>52</sup>	Spain	Quantitative (Cross- sectional study)	Outpatient	145		The purpose to identify potential factors in- fluencing adherence to antide- pressant treatment by patients with mood disorders in the commu- nity mental health care setting.	Socio- demographic character- istics and clinical variables, medica- tion adherence, attitudes toward treatment, beliefs about medica- tion, attitude toward concor- dance, depressive symp- toms, and side effect

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
De Las Cuevas et al. (2014) <sup>53</sup>	Spain	Quantitative (Cross-sectional study)	Outpatient	119		The purpose to examine the relationship of psychological reactance, health locus of control and the sense of self-efficacy on adherence to treatment regimen among psychiatric outpatients with depression.	Socio-demographic characteristics and clinical variables, medication adherence, psychological features (psychological reactance, health locus of control, and self-efficacy)
Isa et al. (2018) <sup>54</sup>	Nigeria	Quantitative (Pre-post one-group intervention study)	Outpatient	18		The purpose to investigate the effects of psycho-education and basic CBT intervention on depressed medication-treated adolescents.	Depressive symptoms, knowledge of depression, hope, attitudes towards treatment adherence, and satisfaction

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Klein et al. (2017) <sup>55</sup>	Netherlands	Quantitative (Descrip- tive longitudi- nal study)	Outpatient	289		The purpose to explore beliefs about the causes of depression and recovery and to examine whether they predict antide- pressant medica- tion use.	Medication adherence, beliefs regarding depres- sion, and antide- pressant medica- tion dosage

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Lu et al. (2016) <sup>56</sup>	China	Quantitative (Cross- sectional study)	Outpatient	135		The purpose to investigate the variables associated with adherence with antide- pressants in elderly Chinese patients, focusing on attitudes and beliefs as potential predictors, as well as sociode- mographic character- istics and illness- related variables.	Medication adherence and beliefs about medication

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Lucca et al. (2015) <sup>57</sup>	India	Quantitative (Cross-sectional study)	Outpatient	400 (n=170 patients with depression)		The purpose to determine the incidence and factors associated with med- ication nonadher- ence among psychi- atric outpatients.	Medication adherence and reasons for medica- tion nonadherence
Novick et al. (2015) <sup>58</sup>	Six East Asian countries and regions (China, Hong Kong, Malaysia, Singapore, South Korea, and Taiwan)	Quantitative (Cross-sectional study, prospec- tive, observa- tional study)	Inpatient	430		The purpose to describe pharmaco- logical treatment patterns in patients with MDD.	Medication adherence, reasons for medica- tion nonadher- ence, depressive symp- toms, somatic symptom, and quality of life

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Serrano et al. (2014) <sup>59</sup>	Spain	Quantitative (Observational and longitudinal study)	Outpatient	29		The purpose to determine the degree of therapeutic adherence in patients with depression, examine factors involved in the adherence process, and observe the clinical outcome.	Medication adherence, depressive symptoms, drug attitude, beliefs about medication, and personality
Shrestha Manandhar et al. (2017) <sup>60</sup>	Nepal	Quantitative (Prospective study)	Inpatient and outpatient	60		The purpose to determine the medication adherence pattern in patients with depression and assess the factors associated with non-adherence to the prescribed antidepressant therapy.	Medication adherence and medication adherence pattern



<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Taleban et al. (2016) <sup>61</sup>	Iran	Quantitative (Random- ized clinical trial)	Outpatient	198	Booklet and text messaging group (67), booklet (66), and control (65)	The purpose to evaluate the impacts of text messaging interven- tions, which aimed to inspire the affected patients to peruse bibliotherapy.	Medication adherence and depression severity
Vannachavee et al. (2016) <sup>62</sup>	Thailand	Quantitative (Random- ized controlled trial with two parallel- group posttest- only designs)	Outpatient	56	(30,26)	The purpose to examine the effect of DAEP on adherence behaviors in patients with first diagnosed major depressive disorder.	Medication adherence and depression severity

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Bushnell et al. (2016) <sup>63</sup>	USA	Quantitative (Retro- spective cohort study)	Inpatient and outpatient	8,837		The purpose to identify predictors of six-month antide- pressant persistence.	Antidepressant persis- tence, demo- graphic, clinical, and psy- chosocial factors (age, sex, psychi- atric and non- psychiatric co- morbidities, healthcare utiliza- tion, antide- pressant class, prior suicide attempt, high and mid- potency prescrip- tion opiate usage, and recurrent MDD diagnosis)

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Green et al. (2017) <sup>64</sup>	USA	Mixed- method	Outpatient	28		The purpose to investigate knowledge and attitudes about antidepressant medication, including risks and benefits, how patients received this information, and how they would prefer to learn about antidepressants.	Medication persistence, knowledge and attitudes about antidepressant medication, Depression, Trauma exposure, post-traumatic stress disorder, and side effects
Grover et al. (2018) <sup>65</sup>	India	Quantitative (Natural- istic, longitudi- nal, follow-up study)	Outpatient	140		The purpose to evaluate the medication adherence, treatment adherence, and outcome of depression.	Medication adherence, treatment adherence, and outcome of depression

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Holvast et al. (2019) <sup>66</sup>	Netherlands	Quantitative (Longitu- dinal study)	Outpatient	1,512		The purpose to determine the non-adherence rates to antidepressants among older adults in primary care, based on non-initiation, suboptimal implementation or non-persistence.	Non-initiation, suboptimal implementation, non-persistence, associated with non-adherence
Klang et al. (2015) <sup>67</sup>	Israel	Quantitative (Prospec- tive, nonran- domized, open- label, naturalis- tic observa- tional study)	Outpatient	4246	(173, 4079)	The purpose to effectiveness of CP intervention for patients with MDD.	Medication adherence and depressive symptoms

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
LeBlanc et al. (2015) <sup>68</sup>	USA	Quantitative (Cluster randomized trial)	Outpatient	Clinicians (117); patients (297)	Clinicians (66, 51); patients (158, 139)	The purpose to estimate the effect of DMC on quality of the decision- making process and depression outcomes.	Patient knowledge and involvement in decision making, patient and clinician decisional comfort and satisfaction, encounter duration, medication adherence, and depression symptoms
Slabbert et al. (2015) <sup>69</sup>	South Africa	Quantitative (Prospec- tive, descriptive cohort study)	Outpatient	14,135		The purpose to investigate the prevalence of antide- pressant non- compliance in the private healthcare sector of South Africa.	Medication adherence

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Zhang et al. (2016) <sup>70</sup>	China	Quantitative (Retro- spective cohort study)	Inpatient and outpatient	8,484		The purpose to investigate medica- tion usage patterns, health care resource utiliza- tion, and direct medical costs of patients with MDD in Beijing, People's Republic of China.	Medication usage patterns, health care resource utiliza- tion, and economic burden
Hammonds et al. (2015) <sup>71</sup>	USA	Quantitative (Random- ized, parallel- group clinical trial)	Outpatient	57	(30, 27)	The purpose to determine the effect of medica- tion reminding via smart- phone app on adherence to antide- pressant medica- tions in college students.	Medication adherence, depres- sion, social support, stress, and health beliefs

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Pradeep et al. (2014) <sup>72</sup>	India	Quantitative (Random- ized trial)	Outpatient	260	(122, 138)	The purpose to investigate effective- ness of enhanced care in improving treatment seeking and adherence to antide- pressant medica- tion in women with depression living in rural India.	Medication adherence, number of clinic visits, depressive symp- toms, and quality of life

<b>Author (year)</b>	<b>Country</b>	<b>Study design</b>	<b>Study setting</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))</b>	<b>Purpose of study</b>	<b>Outcome variables</b>
Srimongkon et al. (2018) <sup>73</sup>	Australia	Qualitative (Phe- nomeno- logical approach)	Outpatient	23		The purpose to explore factors which facilitate and negatively impact adherence, at initiation, implemen- tation and discontin- uation phases of adherence to antide- pressant medication.	Facilitate and negatively impact adherence



Author (year)	Country	Study design	Study setting	Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))	Sample (Participant no. (Inter- ventional, Control) Patient characteris- tics (age, gender))	Purpose of study	Outcome variables
Vargas et al. (2015) <sup>74</sup>	USA	Qualitative (Ethnography)	Outpatient	30		The purpose to examines salient views of depression and pharma- cotherapy among Latinos seeking outpatient antide- pressant therapy and suggests possible strategies for engaging patients on these views prior to the onset of treatment.	Views of depression and antide- pressant medication

**\*\*Note:** CBT: Cognitive Behavioural Therapy; CP: Community pharmacist; DAEP: Drug Adherence Enhancement Program; DMC: Depression Medication Choice; MDD: Major Depressive Disorder; SDM: Shared Based on Decision Making; TIP: The Treatment Initiation and Participation

**Table 2 .** Quality of Studies by Mixed Methods Appraisal Tool (MMAT) (n = 36)

Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies
<b>Criteria</b> <b>Author</b> <b>(year)</b>	Is the qualitative approach appropriate to answer the research question?	Are the qualitative data collection methods adequate to address the research question?	Are the findings adequately derived from the data?	Is the interpretation of results sufficiently substantiated by data?	Is there coherence between qualitative data sources, collection, analysis and interpretation?	<b>MMAT score</b>
Ho et al. (2017) <sup>24</sup>						100
Srimongkon et al. (2018) <sup>73</sup>						100
Vargas et al. (2015) <sup>74</sup>						100
<b>Quantitative Randomized Controlled Trials</b> <b>Criteria</b> <b>Author</b> <b>(year)</b>	<b>Quantitative Randomized Controlled Trials</b> Is randomization appropriately performed?	<b>Quantitative Randomized Controlled Trials</b> Are the groups comparable at baseline?	<b>Quantitative Randomized Controlled Trials</b> Are there complete outcome data (80% or above)?	<b>Quantitative Randomized Controlled Trials</b> Are outcome assessors blinded to the intervention provided?	<b>Quantitative Randomized Controlled Trials</b> Did the participants adhere to the assigned intervention (80% or above)?	<b>Quantitative Randomized Controlled Trials</b> <b>MMAT score</b>
Sirey et al. (2017) <sup>19</sup>						100
Aljumah & Hassali (2015) <sup>47</sup>						100
Taleban et al. (2016) <sup>61</sup>				x		75
Vannachavee et al. (2016) <sup>62</sup>				x		75
LeBlanc et al. (2015) <sup>68</sup>				x		75
Hammonds et al. (2015) <sup>71</sup>				x		75
Pradeep et al. (2014) <sup>72</sup>						100
<b>Quantitative Non-Randomized Studies</b>	<b>Quantitative Non-Randomized Studies</b>	<b>Quantitative Non-Randomized Studies</b>	<b>Quantitative Non-Randomized Studies</b>	<b>Quantitative Non-Randomized Studies</b>	<b>Quantitative Non-Randomized Studies</b>	<b>Quantitative Non-Randomized Studies</b>

Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies
<b>Criteria</b>	Are the participants representative of the target population?	Are measurements appropriate regarding both the outcome and intervention (or exposure)?	Are there complete outcome data?	Are the confounders accounted for in the design and analysis?	During the study period, is the intervention administered (or exposure occurred) as intended?	<b>MMAT score</b>
<b>Author (year)</b>						
Bhat et al. (2018) <sup>49</sup>						100
Isa et al. (2018) <sup>54</sup>				x		75
Klang et al. (2015) <sup>67</sup>		x		x		50
<b>Quantitative Descriptive Studies</b>	<b>Quantitative Descriptive Studies</b>	<b>Quantitative Descriptive Studies</b>	<b>Quantitative Descriptive Studies</b>	<b>Quantitative Descriptive Studies</b>	<b>Quantitative Descriptive Studies</b>	<b>Quantitative Descriptive Studies</b>
<b>Criteria</b>	Is the sampling strategy relevant to address the research question?	Is the sample representative of the target population?	Are the measurements appropriate?	Is the risk of nonresponse bias low (60% or above)?	Is the statistical analysis appropriate to answer the research question?	<b>MMAT score</b>
<b>Author (year)</b>						
Alekhyia et al. (2015) <sup>21</sup>			x	x		50
Abegaz et al. (2017) <sup>22</sup>						100
Al-Jumah et al. (2014) <sup>23</sup>						100
Yau et al. (2014) <sup>25</sup>						100
Mert et al. (2015) <sup>34</sup>			x			75
Al-Jumah et al. (2014) <sup>46</sup>						100
Baeza-Velasco et al. (2019) <sup>48</sup>						100
Burnett-Zeigler et al. (2014) <sup>50</sup>						100
Chatterjee et al. (2017) <sup>51</sup>				x		75
De las Cuevas et al. (2014) <sup>52</sup>						100

Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies	Qualitative Studies
De Las Cuevas et al. (2014) <sup>53</sup>						100
Klein et al. (2017) <sup>55</sup>				x		75
Lu et al. (2016) <sup>56</sup>						100
Lucca et al. (2015) <sup>57</sup>						100
Novick et al. (2015) <sup>58</sup>			x			75
Serrano et al. (2014) <sup>59</sup>		x		x		50
Shrestha Manandhar et al. (2017) <sup>60</sup>		x	x	x		25
Bushnell et al. (2016) <sup>63</sup>			x			75
Grover et al. (2018) <sup>65</sup>			x	x		50
Holvast et al. (2019) <sup>66</sup>				x		75
Slabbert et al. (2015) <sup>69</sup>				x		75
Zhang et al. (2016) <sup>70</sup>						100
<b>Mixed Methods Studies Criteria Author (year)</b>	<b>Mixed Methods Studies</b>	<b>Mixed Methods Studies</b>	<b>Mixed Methods Studies</b>	<b>Mixed Methods Studies</b>	<b>Mixed Methods Studies</b>	<b>Mixed Methods Studies</b>
	Is there an adequate rationale for using a mixed methods design to address the research question?	Are the different components of the study effectively integrated to answer the research question?	Are the outputs of the integration of qualitative and quantitative components adequately interpreted?	Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?	Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?	<b>MMAT score</b>
Green et al. (2017) <sup>64</sup>					x	75

=yes; x=no; o=can't tell; MMAT=Mixed Methods Appraisal Tool; All studies go through quality assessment passed the screening questions: 1) Are there clear research questions? 2) Do the collected data allow to address the research questions?

**\*\*\*Notes on study limitations using mixed methods appraisal tool (MMAT) criteria**

**Table 3.** Study Design and Quality of Included Studies (n = 36)

Study design	Study no. (%)	MMAT score	MMAT score	MMAT score	MMAT score
		0	25	50	75
Qualitative Studies	3 (8.3)	-	-	-	-
Quantitative Randomized Controlled Trials	7 (19.5)	-	-	-	4
Quantitative Non-Randomized Studies	3 (8.3)	-	-	1	1
Quantitative Descriptive Studies	22 (61.1)	-	1	3	7
Mixed Methods Studies	1 (2.8)	-	-	-	1
<b>Study no. (%)</b>	<b>Study no. (%)</b>	-	1 (2.8)	4 (11.1)	13 (36.1)

**Table 4.** Medication Adherence Rate and Adherence Measurement Methods of Included Studies (n= 33)

Author (year)	Period of data collection	Medication adherence rate (I:C)	Adherence measure	Data collection methods
Sirey et al. (2017) <sup>19</sup>	3 years	The 5-fold increase in adherence during the first 6 weeks of care	BMQ	Self-Report
Alekhyia et al. (2015) <sup>21</sup>	6 months	30.1%	DAI	Self-Report
Abegaz et al. (2017) <sup>22</sup>	4 months	10.6%	MMAS (8-items)	Self-Report
Al-Jumah et al. (2014) <sup>23</sup>	5 months	47.1%	MMAS (8-items)	Self-Report
Yau et al. (2014) <sup>25</sup>	1 year	54%	The prescription record and also the electronic and written medical records (filled prescriptions for any antidepressants with no gaps of >15 days within 6 months after initiation of treatment)	Claims Database

Author (year)	Period of data collection	Medication adherence rate (I:C)	Adherence measure	Data collection methods
Mert et al. (2015) <sup>34</sup>	1 year	69.2%	Not taking any medicine for at least 1 week during the 6-month term before the study was regarded as medication nonadherence; from first-degree relatives and patient files.	Self-Report and patient record
Al-Jumah et al. (2014) <sup>46</sup>	5 months	47.1%	MMAS (8-items)	Self-Report
Aljumah and Hassali (2015) <sup>47</sup>	6 months	NM	MMAS (8-items)	Self-Report
Baeza-Velasco et al. (2019) <sup>48</sup>	NM	29.7%	MARS	Self-Report
Bhat et al. (2018) <sup>49</sup>	5 months	81%	Unstructured scale contains one question	Self-Report
Burnett-Zeigler et al. (2014) <sup>50</sup>	4 months	NM	BMQ	Self-Report
Chatterjee et al. (2017) <sup>51</sup>	NM	NM	MMAS (8-items)	Self-Report
De las Cuevas et al. (2014) <sup>52</sup>	8 months	53.8%	MGLS (4-items)	Self-Report
De Las Cuevas et al. (2014) <sup>53</sup>	4 months	49.6%	MGLS (4-items)	Self-Report
Isa et al. (2018) <sup>54</sup>	2 months	NM	Attitude to Medication Adherence Questionnaire	Self-Report
Klein et al. (2017) <sup>55</sup>	NM	51.9%	MGLS (4-items)	Self-Report
Lu et al. (2016) <sup>56</sup>	9 months	37.8%	MGLS (4-items)	Self-Report
Lucca et al. (2015) <sup>57</sup>	1 year	58.2%	MARS	Self-Report

Author (year)	Period of data collection	Medication adherence rate (I:C)	Adherence measure	Data collection methods
Novick et al. (2015) <sup>58</sup>	7 months	Patient-reported: 42.5%; clinician-reported: 85.4%	-Clinicians were asked to provide their opinion on whether the patient had been adherent with the prescribed medication(s) for MDD since the baseline visit. -Patients were asked how regularly they took the medications prescribed for MDD since the baseline visit.	Self-Report
Serrano et al. (2014) <sup>59</sup>	6 months	72.4%	SMAQ	Self-Report
Shrestha Manandhar et al. (2017) <sup>60</sup>	4 months	37%	Structured questionnaire	Self-Report
Taleban et al. (2016) <sup>61</sup>	NM	NM	MARS	Self-Report
Vannachavee et al. (2016) <sup>62</sup>	3 months	I: 41.17±2.87; C: 22.58±17.07	SMIR	Self-Report
Bushnell et al. (2016) <sup>63</sup>	6 months	45%	Non-persistent if treatment had been stopped before 180 days after the index antidepressant's dispensing date	Medical and pharmaceutical Claims Database
Green et al. (2017) <sup>64</sup>	NM	54%	Medical Record	Claims Database
Grover et al. (2018) <sup>65</sup>	1 year	3 months (34.3%) 3-6 months (25%) 6-12 months (10%)	Medical record	Claims Database

Author (year)	Period of data collection	Medication adherence rate (I:C)	Adherence measure	Data collection methods
Holvast et al. (2019) <sup>66</sup>	2 years	Initiation: 86.5% Optimal implementation: 84.8% Persistence: 62.9%	Three measures of non-adherence (Non-initiation (not dispensed by the SFK database within 14 days), suboptimal implementation (MPR), Non-persistence (discontinuation within 294 days after first dispense))	Claims Database electronic medical records
Klang et al. (2015) <sup>67</sup>	24 weeks	I:55%; C:15.2%	The prescription fill method to assess adherence (the proportion of compliance during the first 24 weeks)	Claims Database
LeBlanc et al. (2015) <sup>68</sup>	2 years	I:67.7%; C:65.5%	PDC	Claims Database
Slabbert et al. (2015) <sup>69</sup>	6 years	34%	MPR	Claims Database
Zhang et al. (2016) <sup>70</sup>	1 year	17.8%	The duration of time from initiation to discontinuation of therapy.	Claims Database
Hammonds et al. (2015) <sup>71</sup>	2 years and 7 months	45%	Percent adherence was calculated by dividing the actual number of pills taken by the expected number of pills taken during the study period and multiplying the total by 100	Pill Count



Author (year)	Period of data collection	Medication adherence rate (I:C)	Adherence measure	Data collection methods
Pradeep et al. (2014) <sup>72</sup>	3 years	I:11.1 ± 10.4; C:3.33 ± 3.79	The total number of weeks the subjects took antidepressant medication, pill counts to ensure that patients took medication as prescribed by doctor.	Pill count

**\*\*Note:** BMQ; The Brief Medication Questionnaire; C: Control; DAI: Drug Attitude Inventory; MARS: The Medication Adherence Rating Scale; MGLS: Morisky Green Levine Medication Adherence Scale; MMAS: Morisky Medication Adherence Scale; MPR: Medicine Possession Ratio; NM: Not Mention; I: Interventional; PDC: Percentage of Days Covered; SMAQ: Simplified Medication Adherence Questionnaire; SMIR: Self-Medication Intake Record

**Table 5 .** Factors affecting toward medication adherence (n=26)

Dimension	Factors in each dimension	Studies
Social-economic factors	Cultural beliefs and attitude of social and family towered mental disorders and medications Stigma of social and family towered mental disorders and medications Level of education Literacy Language Social support networks system (family, friend, spouse, co-worker) Religion beliefs Income Employment status (Nature of the job, occupation of patients) Living conditions	21, 24, 25, 52, 56, 57, 60, 64, 65, 73, 74

Dimension	Factors in each dimension	Studies
Healthcare provider/System-related factors	Accessibility to healthcare services (long distance, lack of accessible appropriate material, limited time and long waiting time at the clinic, and poor access to healthcare locations) Follow-up visits system (Frequent or infrequent follow-ups clinic visits) Instruction and information about medications and disorders Change and multiple prescribers Supply of medications (availability of medication, frequent medication refill) Patient-provider relationship Availability of providers	21-25, 49, 57, 64, 65
Illness-related factors	Onset of the illness Duration of illness Symptoms and illness severity Number of psychiatric hospitalizations Comorbid illness Suicide ideation and attempts Family and past history	21-25, 34, 48, 56, 57, 65, 66, 73
Medication-related factors	Complex treatment regimens Adverse reactions Duration of treatment Cost of treatment Classes of antidepressant	21, 24, 25, 34, 48, 49, 52, 57, 58, 60, 62, 64-66, 69, 73, 74
Patient-related factors	Sociodemographic factors Age Gender Race Marital status Psychological factors Beliefs Attitudes Satisfaction Knowledge Self-management Psychological reactance Locus of control Insight Self-stigma Self-motivation Physical (cognitive and behavioral) factors Forgetfulness The patient's personal obligations Carelessness Confusion	21-25, 34, 46, 48, 49, 51-53, 56, 57, 59, 60, 62, 64-66, 69, 73, 74

**Table 6 .** Studies with interventions to medication adherence (n=10)

Author (year)	Country	Intervention	Categories	Outcomes
Sirey et al. (2017) <sup>19</sup>	USA	TIP Program	Multi-faceted (Cognitive education and information; and behavioral counselling)	TIP Program is an effective intervention to improve early adherence to pharmacotherapy. Also, interventional group were 5 times more likely to be adherent at 6 weeks and were 3 times more likely to be adherent to their antidepressant pharmacotherapy at both 6 and 12 weeks. Furthermore, interventional group showed a significant reduction in depressive symptoms.

Author (year)	Country	Intervention	Categories	Outcomes
Aljumah and Hassali (2015) <sup>47</sup>	Saudi Arabia	Pharmacist interventions SDM	Education and information	Pharmacist interventions based on SDM, intervention group showed significant differences in adherence to medication, treatment satisfaction, general overuse beliefs, specific concern beliefs, and total general beliefs about medicines. However, severity of depression and quality of live were not significantly change between intervention and control group at the end of six months. After 6 months, intervention group patients showed statistically significant in adherence to antidepressants and treatment satisfaction, and a decrease in concern beliefs and general beliefs about medicines.

Author (year)	Country	Intervention	Categories	Outcomes
Bhat et al. (2018) <sup>49</sup>	USA	A pharmacist-led multidisciplinary telemonitoring service	Multi-faceted (Education and information; and monitor feedback (adherence and disease))	The clinical pharmacist-led multidisciplinary antidepressant telemonitoring service is a resource to monitor patients after antidepressant initiation or uptitration in primary care settings and provided interventions for patients. However, unable to strongly assess the impact of clinical pharmacists' interventions.
Isa et al. (2018) <sup>54</sup>	Nigeria	Psycho-education and basic CBT strategies	Multi-faceted (Cognitive education and information; and behavioral counselling)	The effect of a psycho-educational and basic CBT intervention resulted in reduction in depressive symptoms, improvements in knowledge of depression, hope, and attitude towards treatment adherence one week and four weeks after the intervention.

Author (year)	Country	Intervention	Categories	Outcomes
Taleban et al. (2016) <sup>61</sup>	Iran	Bibliotherapy and text messaging	Counselling (Cognitive behavioral interventions)	Based on treatment compliance not significantly affected through group, but factors interactive effect of group factor and the time factor was statistically significant. Neither of the groups showed significant variations of the treatment compliance in different times comprising before the treatment, after the treatment or during the following up procedure. However, intensity of depressive symptoms was significantly affected through time and group factors as well as time-group interaction. Neither of the interventional groups differed in intensity of depressive symptoms.

Author (year)	Country	Intervention	Categories	Outcomes
Vannachavee et al. (2016) <sup>62</sup>	Thailand	DAEP	Multi-faceted (Motivational interviewing; and cognitive and behavioral counselling)	The participants in the experimental group had more correct drug adherence behaviors in terms of the dosage and timing during the sixth week than that of the participants in the control group. Also, the patients who received the DAEP had better depression scores after the intervention than those who received only the usual care.
Klang et al. (2015) <sup>67</sup>	Israel	CPs management	Multi-faceted (Education and information, reminders, and monitor feedback (adherence and disease))	Measure adherence to antidepressant treatment at 6 months. At 1 month, the adherence rate was 71% in the CP group and at 6 months, the rates were high (55%) than control group of 42%. At 1 month, the adherence rate was 57% in the control group and at 6 months, the rate was 15.2%.

Author (year)	Country	Intervention	Categories	Outcomes
LeBlanc et al. (2015) <sup>68</sup>	USA	DMC	Education and information	The use of DMC by primary care clinicians and patients with moderate to severe depression during clinical encounters was feasible and effectively improved patient knowledge and engagement in the decision-making process, as well as patient and clinician satisfaction with that process. However, use of the decision aid, had no discernible effect on encounter duration, depression control, and medication use and adherence.
Hammonds et al. (2015) <sup>71</sup>	USA	Electronic medication reminder application	Reminders	Participants use of a medication reminder app were 3.5 times more likely to adhere to their medication regimen than those in the control group. However, depression symptoms were reduced from baseline, but the magnitude of change was not greater in participants using the medication reminder app.



Author (year)	Country	Intervention	Categories	Outcomes
Pradeep et al. (2014) <sup>72</sup>	India	Community care support	Multi-faceted (Education and information; and monitor feedback (adherence and disease))	The number of clinic related visits and the duration of treatment (as measured by the number of weeks that subjects took antidepressant medication) was significantly greater in the interventional group compared to control group. While there was a significant difference in the treatment adherence pattern between the two groups, there was no significant difference in the outcomes of depression and quality of life at six months follow up.

**\*\*Note:** CBT: Cognitive Behavioural Therapy; CP: Community pharmacist; DAEP: Drug Adherence Enhancement Program; DMC: Depression Medication Choice; SDM: Shared Based on Decision Making; TIP: The Treatment Initiation and Participation

**Figure 1 .** PRISMA flow diagram of search and selection process