Journal of Pharmacy

Journal of Pharmacy

Assessment of Methods to Measure Adherence of Antidepressants: A Systematic Review

Nur Aina Abdul Ghafur[1], Syahrir Zaini[1,2], and Hussam Abdeljabar Ahmad Mizher[1,2*]

1Department of Pharmacy Practice, Kulliyyah of Pharmacy, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.

2Kulliyyah of Pharmacy, Quality Use of Medicines Research Group, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.

Abstract

Introduction: Adherence towards antidepressant agents is a vital element in effectively managing depression. Non-adherence of antidepressants can lead to a recurrence of depressive symptoms and decreased treatment effectiveness. Adherence is assessed using various types of measures. This study aims to evaluate the different methods used to assess the adherence towards antidepressants on adults with depression**. Method:** "This systematic review adhered to the guidelines outlined in the PRISMA statement. "PubMed, Cochrane Library, and Scopus are searching from 2013 to 2023 for articles that studied or reported on antidepressant adherence measures in adults with depression. Two authors conducted independent screenings of the articles against the eligibility criteria, examining titles, abstracts, and full texts. "The risk of bias for all included studies were assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists. "Information from all the selected articles was extracted using a predefined table. **Results:** 15 studies met the eligibility criteria. When measuring adherence towards antidepressant at initiation and/or implementation phase, "self-report methods such as Medication Adherence Rating Scale (MARS) demonstrated acceptable reliability and validity, while Brief Medication Questionnaire (BMQ by Svarstad et al.), Morisky Medication Adherence Questionnaire (MAQ), and Brief Adherence Rating Scale (BARS) showed good validity, and Morisky Medication Adherence Scale (MMAS), Morisky Green Levine Adherence (MGLA), Beliefs about Medicine Questionnaire (BMQ by Horne et al.) and Drug Attitude Inventory (DAI-10) showed good reliability." **Conclusion**: This study found a diverse range of methods to measure adherence towards antidepressant in adults. Self-report assessments, particularly in primary care and psychiatric settings, emerged as the most practical tools followed by clinician-rating scale, pharmacy refill data, adherence scale, pill count, and average serum level. No single measure with consistently shown strong reliability and validity across different adherence stages, highlighting the need for a combined approach.

Article history:

Received: 18 Feb 2024
Accepted: 11 Mar 2024
Published: 31 July 2024

Keywords:

Antidepressant
Adherence
Depression
Methods

doi: 10.31436/jop.v4i2.287

*Corresponding author's email: hussam@iium.edu.my

Introduction

Depression is a highly widespread mental health illness worldwide, and the utilization of antidepressants is considered a fundamental component in it's -management. Depression is one ofpsychiatric condition marked by prolonged sadness and a reduced motivation in engaging in pleasurable activities (Chand & Arif, 2021). Depressive illnesses are characterized by persistently feelings of sadness, emptiness, or irritabilities, for constant two weeks duration, which associated with physical and mental changes that would substantially influence functional abilities on individuals (Ormel et al., 2019).

Compliance with pharmacological regimeis crucial towards the successful management of major mental illness such as depression. Adherence is defined as the degree to which an individual's behaviours correlate with health-related instructions or suggestions provided by a healthcare professional in relation to a particular disease or disorder condition (Gast & Mathes, 2019). The lack of adherence on following instruction of treatments has been found to be associated with a deterioration in mental well-being and an increased likelihood of experiencing relapse of depressive symptoms (Stewart et al., 2022).

When examining the rates of non-adherence towards antidepressant medication over a six-month period, it is seen that there is a little difference between psychiatric groups (52%) and primary care populations (46.2%). It indicates around 50% of patients showed non-adherence towards antidepressant medication regardless of whether they are from primary or psychiatric care settings (Sansone & Sansone, 2019). On the other hand, the prevalence of non-adherence in older individuals in the United States varies from 29% to 40% "(Sirey et al., 2017).

Research undertaken in both primary care and psychiatric settings has revealed that most patients with diagnosis of major depressive disorder (MDD) show poor compliance to their antidepressant. It shows that a significant proportion of individuals diagnosed with MDD exhibit poor compliance towards antidepressant (Dell'Osso et al., 2020). While the importance of adherence is well-established, the choice of measurement method is a critical factor in understanding and addressing this issue. The "gold standard" for evaluating medication adherence has not been established yet. Hence, choosing between at least two approaches whether direct or indirect methods can produce more accurate outcome. (Jimmy & Jose, 2020).

Multiple measurements with various methods are employed to evaluate adherence towards antidepressant medication. These may encompass self-report questionnaires, electronic monitoring, pharmacy refill data, and clinical assessments (Lam & Fresco, 2015). These measurements offer some assistance in determining how closely patients adhere to their prescription schedule or prescribed medication regime. Different adherence measures may lead to variability in adherence reports, incomparable adherence outcomes, thus, it causes the elevation of an inaccurate conclusion. Therefore, this systematic review aims to evaluate the different methods used to assess the adherence of antidepressants by using different objective and subjective measures.

"The introductory section plays a crucial role in contextualising the study and underscoring its significance. State briefly the purpose, and rationale for the study or observation. Avoid a review of the subject by confining to only relevant information and references. Do not include data or conclusions from the work being cited. Citations are written according to **APA 7th style.** Kindly refer to the example of references in this template. Examples of in-text citations (Almanasef, 2021; Chang *et al*., 2020; Chung *et al*., 2021; Devraj *et al*., 2019; Liu *et al*., 2022; Martí-García *et al*., 2023; Morse, 2000; Zaini *et al*., 2018).

Materials and methods

Methods

Protocol

Articles published from January 2013–November 2023. These databases were searched for articles that studied or reported on antidepressant adherence

measures among people with depression

Search Strategy

This systematic study followed the guidelines and fundamental principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021)."The principal source of literature was from electronic bibliographic databases using a comprehensive search strategy. Three databases; PubMed, Library Cochrane and Scopus were searched for articles.

The search medical subject headings (MeSH) phrases for four key domains were combined: adherence, antidepressant, depression, and methods. Domain one included keywords: adherence, compliance, nonadherence, non-adherence, noncompliance, and non-compliance. Domain two included keywords: antidepressant, antidepressive agents, and antidepressant medicines. Domain three included keywords: depression, major depressive disorders, unipolar depression, and bipolar depression. Domain four included keywords: methods, techniques, procedures, and measures. These four domains were joined together using Boolean operators such as "OR" or/and "AND" to make sure the search strategy used was efficacious.

Eligibility criteria

This systematic review examined the eligibility criteria for the articles. Articles were included based on inclusion criteria such as the aged between 18 years and above. The article evaluated about antidepressant adherence in adults with depression were also included. Study design was not limited to only randomised controlled trial (RCT) however other study designs such as cohort, cross-sectional, and quasi-experimental" studies are also included. Furthermore, only studies that published in English Language were included for better data sources extraction. This review excluded studies with participants whomwith other types of comorbidities, children oradolescents, and pregnant women. If the studies reported about antidepressant adherence measured in depression with comorbidity, the studies were also excluded. Further exclusion criteria include study protocols, conference proceedings, editorials, or letters and non-English Language published articles.

Study selection

The first reviewer systematically searched for articles in accordance with the PRISMA guidelines. At first, the papers were evaluated by examining their titles. If the titles indicated a connection to the study's objectives, abstracts were further examined for more details. Upon confirming that the abstracts satisfied the eligibility requirements, full-text articles were obtained to extract farther information. Duplicate articles were removed using Mendeley. The first reviewer conducted the primary data extraction, while the second reviewer verified and validated the qualifying articles by cross-checking. All discrepancies were addressed and discussed as necessary.

Data extraction

Data extracted from the studies include various key elements, such as authors, year publication, study region, study setting (e.g. psychiatric wards, primary care settings), study design (e.g. whether it was a randomised controlled trial), duration that subjects were followed-up, method to measure medication adherence, "psychometric properties of these measures, outcome of adherence, "group of the subjects, and specific phase of adherence. The systematic review employed the adherence phase framework as outlined. We classified studies into specific adherence phases. The initiation phase addressed participants newly prescribed or initiating antidepressant therapy. The implementation phase scrutinised adherence among those who had initiated antidepressant treatment. The discontinuation phase investigated medication adherence when patients ceased taking antidepressant medications (Vrijens et al., 2012).

Risk of bias in individual studies

The risk of bias for all included studies were assessed using the Joanna Briggs Institute (JBI) critical

appraisal checklists (Joanna Briggs Institute, 2017). Scores of '1' were given if the studies fulfil the stated criteria of the checklist, '0.5' if unclear, and '0' if not. After that, the total score was calculated and converted into percentage. Studies with a percentage <50% were categorised as having a high risk of bias, indicative of a low study quality. For percentages falling within the range of 50% to 70%, a moderate risk of bias was assigned, implying a moderate study quality. Conversely, studies attaining a percentage >70% were designated as possessing a low risk of bias, indicative of a high study quality. Any disagreements will be discussed between the two authors. The results were then visualised as traffic-light plots by using "Risk-of-bias VIsualization (robvis) tool (McGuinness and Higgins, 2020)."

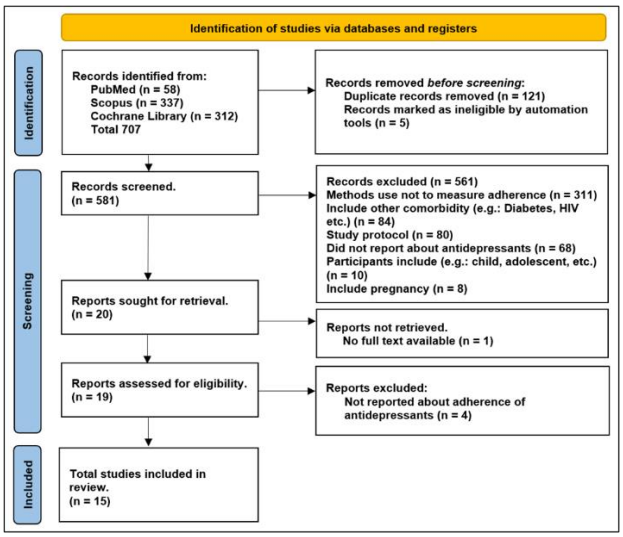

Fig. 1: Flowchart of the study selection process

Outcome of interest

Validity refers to the extent to which a tool accurately measures the intended target of assessment. Meanwhile, reliability pertains to the degree of consistency in findings when an experiment, test, or other measuring technique is performed multiple times (Asunta et al., 2019). Additionally, various psychometric properties, such as correlation or concordance between different adherence measures, were examined in studies. The findings were presented in a structured manner, consisting of a summary of the results and an evaluation of the reliability and validity of the measurements. Following that, the text provided a comprehensive account of the frequency of use for various assessment methods in evaluating adherence to antidepressants in patients with depression.

Results and discussion

Study selection

A total number of 707 studies were in the databases used. Through this search, a total of 15 studies that satisfied the criteria were identified as suitable for inclusion in this systematic review. The search followed PRISMA guidelines shown in Figure 1.

Study characteristics

The four research designs used in the included studies were all published between 2014 and 2023. Most of them took place in psychiatric care"(Aljumah et al., 2014; Warden et al., 2014; Aljumah & Hassali, 2015; Novick et al., 2015; Marasine et al., 2020; Chauhan et al., 2021; Teeng et al., 2021; Yusuf et al., 2021; Ruetsch et al., 2022),"and primary care"settings.(Burnett-Zeigler et al., 2014; Warden et al., 2014; Sirey et al., 2017; Wikberg et al., 2017)". Other studies carried out in the medical centre (Leggett et al., 2015), the research centre (Rossom et al., 2016), and community pharmacies (Shoji et al., 2023).

Out of fifteen studies, twelve of them used one adherence measure to assess antidepressant adherence except 2 studies "(Aljumah & Hassali, 2015; Ruetsch et al., 2022), and one study (Chauhan et al., 2021) used two and five adherence measures respectively. Furthermore, most research employed subjective measurements, except one study (Rossom et al., 2016) that solely utilized objective measures, and two studies used both adherence measures to assess antidepressant adherence "(Chauhan et al., 2021; Ruetsch et al., 2022)."

There are five studies focused on antidepressant adherence at the initiation phase"(Burnett-Zeigler et al., 2014; Aljumah & Hassali, 2015; Novick et al., 2015;

Sirey et al., 2017; Teeng et al.,2021)"while other five studies focused on the implementation phase"(Aljumah et al., 2014; Marasine et al., 2020; Chauhan et al., 2021; Yusuf et al., 2021; Ruetsch et al., 2022)."On the other hand, four out of fifteen studies assessed adherence at both initiation and implementation phase"(Leggett et al., 2015; Rossom et al., 2016; Wikberg et al., 2017; Shoji et al., 2023)."Table 1 provided a summary of the measures used in this systematic study. Table 2 showed the psychometric properties of adherence measures."

Risk of bias within studies

There are four study designs included in this review such as randomized clinical/controlled trial (RCT) (n = 5), quasi-experimental (n = 4), cohort (n = 2), and cross-sectional studies (n = 4). From all the 15 studies included in the review, 14 articles showed a high number of positive responses to the JBI tool's questions, indicating low risk of bias, while only one article had a moderate risk of bias. The evaluation of the included studies is shown in Figures 2a to 2d.

Adherence measures

Multiple adherence measurements have been utilized to assess the adherence of antidepressant medication. Self-report measures were frequently employed in research. The second most often used measure was the clinician-rating scale and pharmacy refill data, followed by the adherence scale, pill count and average serum level. Medication adherence was only evaluated in 14 studies during the initiation and/or implementation phase. There was no data about the adherence phase provided in 1 study (Warden et al., 2014). Moreover, no information on the antidepressants' discontinuation phase was presented in any of the included studies.

Psychometric properties of adherence measures

The psychometric characteristics of certain measures of adherence to antidepressant were assessed by employing the reliability and validity data. The predominant method employed to evaluate reliability was the utilization of Cronbach's alpha, which evaluates internal consistency. Meanwhile, the validity of the measures was evaluated by comparing them with Medication Event Monitoring Systems (MEMS) "(Burnett-Zeigler et al., 2014; Leggett et al., 2015; Sirey et al., 2017)."

Objective adherence measures

In this study, objective measures such as pharmacy refill data, pill count, and serum levels were utilized. Pharmacy refill data were used in two studies (Rossom et al., 2016; Ruetsch et al., 2022), and one study (Chauhan et al., 2021) used pill count and average serum levels. However, both studies did not report any psychometric properties. Antidepressant adherence was measured using clinic-based pill count where the carers were instructed to save and collect any medicine strips that patients had consumed over a period of three months. This measure often misclassified adherent patients as nonadherent, although it was effective at identifying nonadherence. Average level of mood stabilizer in plasma/serum level/ blood concentration of patients were also reported which showed the accuracy in determining nonadherence, with a relatively high capability to identify adherence.

Subjective adherence measures

Studies conducted between 2014 and 2023 consistently showed that self-reporting was the dominant and ongoing method used to subjectively assess adherence to antidepressants. Self-reports are tools that ask patients about their experiences using medications (Rickles et al., 2023). Some examples of self-reported assessments include the Brief Medication Questionnaire (BMQ), Morisky Medication Adherence Scale (MMAS), Drug Attitude Inventory, (DAI-10), clinician-rating scale and many more. However, this method may yield inaccurate results due to potential biases introduced by patients. For instance, patients may provide inaccurate information on questionnaires and diaries, or deliberately manipulate their medication intake by

Table 1*:* Summary of adherence measures.

No	Authors, year	Method to measure adherence			Reliability			Validity			Adherence phase
		Objective	Subjective	n	Provided data	Referred to other	No data	Provided data	Referred to other	No data	
1	Aljumah et al., 2014		/	1			/			/	Implementation
2	Burnett-Zeigler et al., 2014		/	1			/		/		Initiation
3	Warden et al., 2014		/	1			/			/	No data reported
4	Aljumah & Hassali, 2015		/	2		/				/	Initiation
			/			/				/	
5	Leggett et al., 2015		/	1			/		/		Initiation and implementation
6	Novick et al., 2015		/	1			/			/	Initiation
7	Rossom et al., 2016	/		1			/			/	Initiation and implementation
8	Sirey et al., 2017		/	1			/		/		Initiation
9	Wikberg et al., 2017		/	1			/			/	Initiation and implementation

10	Marasine et al., 2020		/	1	/					/	Implementation
11	Chauhan et al., 2021		/	5			/	/			Implementation
			/				/	/			
			/				/	/			
		/					/	/			
		/					/	/			
12	Teeng et al., 2021		/	1			/		/		Initiation
13	Yusuf et al., 2021		/	1		/			/		Implementation
14	Ruetsch et al., 2022	/		2			/			/	Implementation
			/				/			/	
15	Shoji et al., 2023		/	1	/					/	Initiation and implementation

n: Number of adherence measures.

Table 1: Psychometric evaluation of antidepressant adherence measures

Type of adherence measures			Reliability	Validity
Objective	**Subjective**	**Method**		
	Burnett-Zeigler et al., 2014 & Leggett et al., 2015	Brief Medication Questionnaire (by Svarstad)	*	Predictive"validity reported when comparing BMQ with dose omissions as measured by MEMS over a 7-day or 30-day period. (Svarstad et al., 1999)"
	Aljumah & Hassali, 2015	Morisky Medication Adherence Scale (MMAS)	Internal consistency (Cronbach's alpha): ● 0.61. (Morisky et al., 1986) ● 0.62. (Brown et al., 2005) ● 0.70. (Interian, 2010) ● 0.83.(Morisky et al., 2008)	*
		Beliefs about Medicine Questionnaire (by Horne)	Internal"consistency (Cronbach's alpha): ● 0.74 (specific-necessity beliefs), ● 0.63 (specific-concern beliefs), ● 0.73 (general-overuse beliefs), and ● 0.70 (general-harm beliefs). (Horne et al., 1999)	*
	Sirey et al., 2017	Brief Medication Questionnaire (BMQ by Svarstad)	*	Self-report measure validated against an electronic bottle cap data (MEMS Cap). (Svarstad et al., 1999)
	Marasine et al., 2020	Morisky Green Levine Adherence (MGLA) score	Internal consistency (Cronbach's alpha): ● 0.80	*
	Teeng et al., 2021	Brief Adherence Rating Scale (BARS)	*	Good sensitivity (73%) and specificity (74%).
	Yusuf et al., 2021	Medication Adherence	Good psychometric properties, and satisfactorily	Validated for use within the Nigerian

		Rating Scale (MARS)	predicts non-adherence.	setting.
	Chauhan et al., 2021	Morisky"Medication Adherence Questionnaire (MAQ)	*	• Specificity, "34-42%; PPVs, 40-44%; and LR negative, 0.70-0.96; indicate better at detecting adherence. • Sensitivity, 63-73%; NPVs, 54-70%; and LR positive, 1.02-1.16; indicate moderate ability to detect nonadherence."
		Drug Attitude Inventory (DAI-10)"	*	
		Compliance Rating Scale (CRS).	*	Good at sensitivity, but low specificity.
Chauhan et al., 2021		Clinic-based pill counts	*	
		Mood-stabiliser levels (Plasma/ Serum level/ blood conc.)	*	Moderately high specificity and PPVs combined with a"high sensitivity (88%) and higher accuracy (55%) in detecting nonadherence, together with a respectably strong capacity to detect adherence."
	Shoji et al., 2023	Drug Attitude Inventory (DAI)-10	The questionnaire's test-retest reliability and internal consistency has been proven for the Japanese translation.	*

* No data reported/available.

PPV:"positive predictive value.

LR: likelihood ratios.

NPV:"negative predictive value.

discarding tablets to create the appearance of adherence to the prescribed regimen.

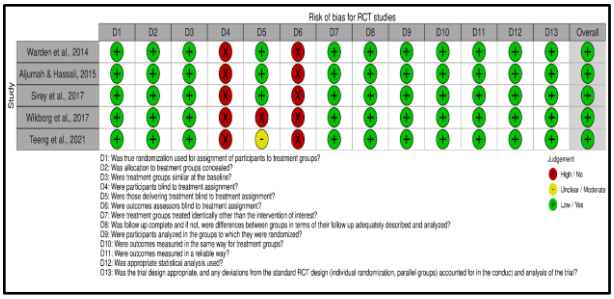

Fig. 2a: Risk of bias for RCT studies.

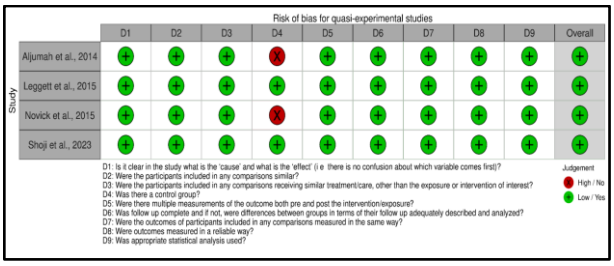

Fig. 2b: Risk of bias for quasi-experimental studies.

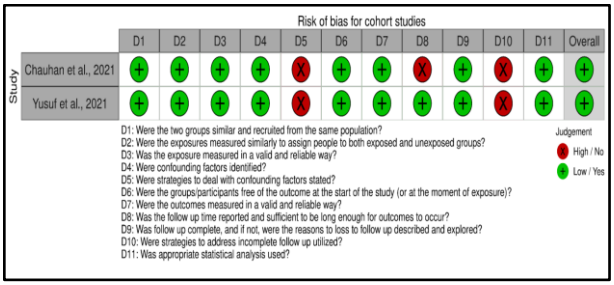

Fig. 2c: Risk of bias for cohort studies.

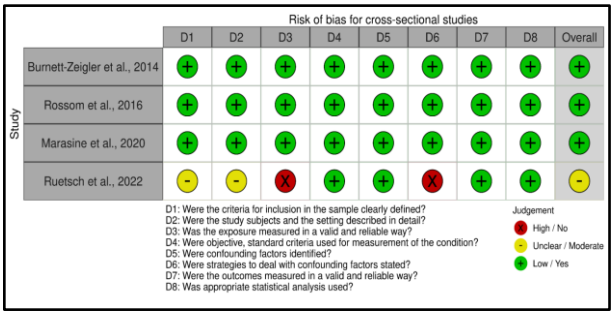

Fig. 2d: Risk of bias for cross-sectional studies.

Brief Medication Questionnaire (BMQ) (Svarstad et al., 1999)

The BMQ, developed by Svarstad, has two components. The first section has three primary components that inquire about patients' adherence to their prescription daily during the week before the interview. Additionally, it evaluates their perceptions of the effectiveness of the treatment and any adverse effects experienced. The second section has 11 questions that inquire about the challenges related to recalling medication-taking habits. It evaluates the obstacles related to physical and cognitive factors that affect adherence and self-confidence. The BMQ has been shown to be valid, with the regimen and belief screens having a sensitivity of 80-100% (Svarstad et al., 1999). Prior research has shown a substantial correlation between this measure and pharmacy refill data (Rickles and Svarstad, 2007). The review revealed that this method has been assessed in three studies (Burnett-Zeigler et al.,2014; Leggett et al., 2015; Sirey et al.,2017)."

Morisky Medication Adherence Scale (MMAS).

The MMAS is an effective screening tool for evaluating the usage of antidepressants. It contains eight items that assess behaviour and adherence to medication, designed to minimize any bias towards agreement. It has a total score ranging from 0 to 8, where higher numbers indicate greater adherence. This self-report questionnaire is a very reliable and validated tool developed by Morisky et al. "(Morisky et al., 1986; Morisky et al., 2008; Krousel-Wood et al., 2009; Morisky & DiMatteo, 2011)."It also has an Arabic version that has been made accessible (Alhalaiqa et al., 2011). The MMAS-8 was utilized in two studies (Aljumah et al., 2014; Aljumah & Hassali, 2015)."

It is a well-established tool for assessing adherence. Its reliability, as indicated by its Cronbach's alpha = 0.61, was reported in the initial research conducted on patients with hypertension "(Morisky et al.,1986)." The reliability of evaluating adherence to antidepressants, particularly during the

implementation period, has been demonstrated to be sufficient, with a Cronbach's alpha of 0.62"(Brown et al., 2005) and 0.70 (Interian, 2010)." This method demonstrates enhanced reliability and validity, especially in hypertension patients. The Cronbach's alpha = 0.83, while the sensitivity is 93%, and specificity is 53% were obtained after evaluating a specified time frame of 2 weeks "(Morisky et al., 2008)." Hence, the MMAS-8 demonstrates strong validity and has been empirically shown to be an effective screening method for assessing adherence to antidepressant treatment, particularly among Arabic patients.

Drug Attitude Inventory, 10-item version (DAI-10).

The DAI-10 questionnaire is a self-report scale consisting of ten items that is widely utilized for the purpose of assessing patients' attitudes regarding medication. Respondents select either true or false to answer each question. The scoring system assigns a value of 1 or −1 to each item, resulting in a total score that can range from −10 (indicating a very low attitude) to +10 (representing the finest possible attitude). Adherence is determined by a positive DAI-10 score, indicating a good subjective attitude, whereas a negative DAI-10 score indicates nonadherence with a poor subjective attitude. Higher scores on the DAI-10 indicate positive opinions towards drugs. This review includes two studies that examined the use of the DAI-10 scale to measure adherence to antidepressant "(Chauhan et al., 2021; Shoji et al., 2023)."

One study demonstrated the effectiveness of certain methods in assessing medication adherence "(Chauhan et al., 2021)." Specifically, they found that the Four-item Morisky Medication Adherence Questionnaire (MAQ) and the DAI-10 (with a higher cut-off) were more accurate in identifying adherence (with a specificity of 34-42%) compared to other measures. These methods also showed a moderate ability to identify nonadherence (sensitivity of 63-73%) when compared to the other measures. Meanwhile, other study has confirmed the internal consistency and test-retest reliability of the Japanese version of the DAI-10 questionnaire "(Shoji et al., 2023)."

Clinician-rating scale

The clinician-rating scale is a subjective assessment tool in which clinicians were asked to express their professional judgement about the patient's adherence to the prescribed antidepressant medication. In a study, the researchers utilized the Clinical Global Impression-Severity scale (CGI-S) (Novick et al., 2015). During this phase, patients were questioned about the consistency of their medication intake for Major Depressive Disorder (MDD) since their first appointment, with four possible answer options. Adherent patients were defined as those who selected option "1" and/or those who took a daily medicine dose within the range of 80% to 120% of the recommended dosage. Meanwhile, other research found that clinicians assessed the adherence of antidepressants using the Compliance Rating Scale (CRS), where higher scores indicate better adherence "(Chauhan et al., 2021)." The results of the study indicated that the CRS had a high level of sensitivity in detecting nonadherence, while demonstrating only moderate agreement with the MAQ.

Other subjective measures

In one study, self-report Adherence Questionnaire (AQ) was used where patients reported on their medication intake over the past 7 days, whether they followed the prescription or adjusted, and specified reasons for these actions "(Warden et al.,2014)." However, this method did not report about the validity or reliability. Next, another study used the Beliefs about Medicine Questionnaire (BMQ by Horne, 1999) to assess patients' medication-related beliefs "(Aljumah & Hassali, 2015)." It consists of two components, namely the BMQ-specific and the BMQ-general. The BMQ's internal consistency reliability has been assessed in patients with

psychiatric conditions.

The Brief Adherence Rating Scale (BARS) is a measure used by clinicians to evaluate adherence. It was described in one research "(Teeng et al., 2021)." The assessment consists of three questions and a visual analogue scale to measure the percentage of dosages taken in the previous month, ranging from 0% to 100%. The BARS assessment showed a high level of sensitivity "73%" and specificity "74%" in accurately identifying outpatients who were not adhering to their prescribed treatment regimen. The BARS used in this investigation was only validated for the administration of oral antipsychotics. In addition, patient self-report Beck Depression Inventory-II (BDI-II) was used to measure depression symptoms in a study "(Wikberg et al., 2017). Adherence to antidepressants is defined when BDI score ≤36 and have the (BDI <13) after 3-month follow-up. However, psychometric properties of this method were not reported.

Furthermore, one study used a Hindi version of the MAQ to assess self-reported adherence over a period of three months "(Aljumah & Hassali, 2015). Due to its well-established sensitivity and specificity in identifying non adherence, MAQ was chosen as the benchmark for the other measurements. Next, another study reported about the reliability of self-report Four-item Morisky Green Levine Adherence (MGLA) which the tool had a Cronbach's alpha of 0.80, indicating strong internal consistency (Marasine et al., 2020)."The MGLA score is a structured instrument consisting of four items. Each item requires a dichotomous answer (yes or no). A low degree of adherence is indicated by a score of 3 or 4, moderate adherence level score = 1 or 2, and high adherence level score = 0.

Yusuf et al. (2021) reported that the Medication Adherence Rating Scale (MARS) is a self-reporting tool consisting of 10 items. Each question requires a 'yes' or 'no' answer. The overall score on the MARS may vary from 0 to 10, with a higher score suggesting more adherence to medicine. The scale has strong psychometric qualities, effectively predicts non-adherence, and has been successfully validated for use in the Nigerian settings. Lastly, a study measures the adherence of antidepressants by using patient report, collateral report, and psychopathology for patients with Bipolar Depression (BD) or Major Depressive Disorder (MDD) "(Ruetsch et al., 2022)." However, no psychometric properties of this measure were reported.

Discussions

The utilization of an adherence measurement tool for adults with depression taking antidepressants holds significant importance in the overall management of the condition. Monitoring adherence provides crucial insights into whether patients are consistently following their prescribed medication regimen. This information is essential for healthcare professionals to assess treatment effectiveness, prevent relapses, and tailor therapeutic strategies, ultimately contributing to improved mental health outcomes and a better quality of life for individuals with depression. Regular use of adherence measurement tools enhances communication between patients and healthcare providers, fostering a collaborative approach in optimizing antidepressant therapy for the well-being of adult patients with depression.

This systematic review assesses the psychometric features of all measures of adherence used to analyse the behaviour of antidepressant consumption in people with depression. In this research, measurements of adherence were specifically focused on two phases: initiation and implementation. The discontinuation phase of pharmacotherapy was not reported. This review classified studies as being in the *"initiation phase of the adherence process"* if they recruited participants who had recently been prescribed antidepressant medications or if the study indicated that participants were starting therapy with antidepressant medications for the first time. Meanwhile, the implementation phase focused on participants who were currently taking the medication, and the discontinuation

phase focused on patients who had stopped taking the medication.

Self-report such as BMQ by Svarstad, pharmacy refill data, BDI-II, and DAI-10 have the capability to measure adherence at more than one adherence phase which can capture both initiation, and implementation of treatment (Leggett et al., 2015; Rossom et al., 2016; Wikberg et al., 2017; Shoji et al., 2023). However, studies by Burnett-Zeigler et al. (2014), and Sirey et al. (2017) capture BMQ by Svarstad on initiation phase only, while Chauhan et al. (2021) used DAI-10 only at implementation phase. The lack of comprehensive data from the recruited studies has made it challenging to determine the adherence phases.

Psychometric properties refer to the validity and reliability of the measurement tool (Asunta et al., 2019). Reliability that included the studies are test-retest reliability and internal consistency. Test-retest reliability pertains to the inherent stability of an assessment across time, evaluating the extent to which the scores obtained from the measuring instrument remain constant over successive test administrations (Berchtold, 2016). Internal consistency evaluates the extent to which the items in the questionnaire effectively measure the same underlying concept. Measures with a value of 0.80 or more are deemed excellent, while the least acceptable value for Cronbach's alpha is 0.7; however, values above 0.6 are also accepted (Griethuijsen et al., 2014; Taber, 2018). Furthermore, the included validity is specifically predictive validity. Confirming predictive validity involves providing evidence that the scale accurately predicts a gold-standard criteria that will be tested at a later point in time (Lazar et al., 2017).

The most frequently employed objective measure was pharmacy refill data (Rossom et al., 2016; Ruetsch et al., 2022), followed by pill count and average serum levels (Chauhan et al., 2021). However, another systematic review reported that MEMS is the predominant objective measure, with pharmacy records being the subsequent commonly utilized method to measure adherence in unipolar depression only. MEMS is widely acknowledged as a benchmark for adherence, often considered a "gold standard" (Srimongkon et al., 2019). Following this, while pill counts are frequently employed to assess adherence in bipolar disorder, their reliability is questionable due to uncertainty about whether the dispensed tablets are taken (Chauhan et al., 2021). Consequently, it is widely suggested that pill counts are only effective when conducted unexpectedly during home visits (Shiomi et al., 2021).

Moreover, average serum level is a direct method measuring the antidepressant or its metabolite concentration in a patient's blood or urine. This method is particularly useful for specific antidepressants that have measurable markers (Cristea et al., 2019). However, this method may not be suitable for certain drugs with extended half-lives that can still be detected in patients even after treatment ends (Anghel et al., 2019). For objective measure, only study by Chauhan et al. (2021) reported about the validity of the tool where it was revealed that pill counts were effective in detecting nonadherence (sensitivity) but were not reliable in detecting adherence (specificity). Additionally, the tool often incorrectly identified patients as non adherent. Although the yields are low, the levels of moodstabilizers in serum or plasma showed a high sensitivity (88%) and greater accuracy (55%) in detecting nonadherence. They also demonstrated a reasonably high ability to detect adherence, with moderately high specificity and positive predictive value.

Self-report measures were often favoured in adherence research and were the most used subjective measure of adherence at both initiation and/or implementation phase. This method may yield inaccurate results due to potential biases introduced by patients. For instance, patients may provide inaccurate information on questionnaires and diaries, or deliberately manipulate their medication intake by discarding tablets to create the appearance of adherence to the prescribed regimen (Anghel et al., 2019).

A commonly used self-report measure was the BMQ by Svarstad et al. Although Svarstad's BMQ psychometric properties have been investigated in other chronic illnesses, only minimal associations with pharmacy refill data have been found. The questionnaire's validity was confirmed by referring it to other data. It found predictive validity when comparing the questionnaire (BMQ) with dose omissions recorded by MEMS over 7-day or 30-day periods (Burnett-Zeigler et al., 2014; Leggett et al., 2015).

MMAS-8 was another self-report measure that was indicated for patients who are taking antidepressant medications for depression, as well as for other medical disorders. It demonstrated acceptable reliability (Cronbach's alpha = 0.61) in research in patients with hypertension, adequate reliability (Cronbach's alpha = 0.62 and 0.70) when assessing adherence to antidepressant medicines at the implementation phase of adherence (Aljumah & Hassali, 2015). This tool also showed better reliability and validity (Cronbach's alpha = 0.83, sensitivity = 93%, and specificity = 53%) albeit in hypertensive patients when considering a specific time frame of 2 weeks.

The BMQ by Horne et al. is another self-report measure that has acceptable internal consistency reliability with Cronbach's alpha = 0.74, 0.63, 0.73, and 0.70 for BMQ specific-necessity beliefs, specific-concern beliefs, general-overuse beliefs, and general-harm beliefs respectively when used as a measure of medication adherence in depression (Aljumah & Hassali, 2015). Studies by Marasine et al. (2020), and Yusuf et al. (2021) reported good reliability for the tools where MGLA score showed internal consistency (Cronbach's alpha = 0.80), and MARS demonstrated good psychometric properties, and satisfactorily predicts non-adherence for measuring adherence of antidepressants in patient with depression.

Out of 15 studies that included, only 9 studies reported the psychometric properties of adherence measures where 3 studies, 5 studies, and 1 study reported reliability, validity, and both properties respectively. It is worth mentioning that past research on medication adherence employed just one measure, but most recent studies now use several measures of adherence (Aljumah & Hassali, 2015; Chauhan et al., 2021; Ruetsch et al., 2022), acknowledging that various measures assess distinct elements of adherence. Since there is no universally accepted "*gold standard*" for adherence evaluation, opting for a dual strategy that incorporates both direct and indirect methods, as suggested by Jimmy and Jose (2020) and Srimongkon et al. (2019), can enhance the accuracy of results.

There are several limitations of this systematic review. Firstly, most of the studies analyzed in this review focused on medication adherence during the initiation and implementation phases. It is important to note that none of the studies specifically examined medication adherence at the discontinuation phase. This highlights a notable gap in the existing research, as there is no data available on the patients who have been prescribed antidepressant medication but have discontinued its use. Secondly, the systematic reviews require substantial time and resources. Hence, it can be challenging to conduct a comprehensive review within limited time frames or with limited resources.

Next, this study specifically examines individuals with depression who do not have any other comorbidity, with the aim of improving the reliability of the results. However, it is important to note that the the findings may be restricted to general population, as they may not apply to individuals with specific types of depression, comorbidity, or adolescents. Lastly, not all the included articles reported about the psychometric properties of the methods to measure medication adherence. This will affect the validity of data for the most reliable and validated method used to measure medication adherence.

Conclusion

In conclusion, the systematic review on the

assessment of methods to measure adherence of antidepressants in adults with depression reveals a utilization of both diverse range objective and subjective measures, particularly during the initiation and implementation adherence phases. Self-report assessments have become the most often used and convenient instruments in primary care and psychiatric settings when assessing antidepressant adherence in adults with depression. They are followed by clinician-rating scales and pharmacy refill data, adherence scales, pill counts, and average serum levels (biological markers). Although an assessment of psychometric properties was conducted, no single standard measure with consistently strong reliability and validity across different stages of adherence was found. This highlights the need of using a comprehensive strategy that incorporates both subjective and objective assessments. Considering the lack of a definitive benchmark as gold standard, it is advisable to use this practical method for evaluating compliance in individuals with depression.

Authors Contributions

The authors, N.A.A.G., H.A.A.M., and S.Z. contributed jointly to the research. Their collaborative efforts involved reviewing and performing literature synthesis to comprehensively assess the various methods must for measuring adherence to antidepressant medications in individuals with depression. Additionally, they provided recommendations for future research, the importance of combining subjective and objective measures for practical adherence assessment in this population need to be emphasize.

Conflict of interest

The authors declare no conflict of interests. This study conducted with transparency and impartiality to ensure the reliability and credibility of the systematic review.

References

Al-Jumah, K., Ahmad Hassali, A., & AlQhatani, S. (2014). Examining the relationship between adherence and satisfaction with antidepressant treatment. Neuropsychiatric Disease and Treatment, 2014:10, 1433–1438. https://doi.org/10.2147/ndt.s67008

Alhalaiqa, F., Deane, K. H. O., Nawafleh, A. H., Clark, A., & Gray, R. (2011). Adherence therapy for medication non-compliant patients with hypertension: a randomised controlled trial. Journal of Human Hypertension, 26(2), 117–126. https://doi.org/10.1038/jhh.2010.133

Aljumah, K., & Hassali, M. (2015). Impact of pharmacist intervention on adherence and measurable patient outcomes among depressed patients: a randomised controlled study. BMC Psychiatry, 15(1). https://doi.org/10.1186/s12888-015-0605-8

Anghel, L. A., Farcas, A. M., & Oprean, R. N. (2019). An overview of the common methods used to measure treatment adherence. Medicine and Pharmacy Reports, 92(2), 117–122. https://doi.org/10.15386/mpr-1201

Asunta, P., Viholainen, H., Ahonen, T., & Rintala, P. (2019). Psychometric properties of observational tools for identifying motor difficulties – a systematic review. BMC Pediatrics, 19(1). https://doi.org/10.1186/s12887-019-1657-6

Berchtold, A. (2016). Test–retest: Agreement or reliability? Methodological Innovations, 9(1), 205979911667287. https://doi.org/10.1177/2059799116672875

Brown, C., Battista, D. R., Bruehlman, R., Sereika, S. S., Thase, M. E., & Dunbar-Jacob, J. (2005). Beliefs About Antidepressant Medications in Primary Care Patients. Medical Care, 43(12), 1203–1207. https://doi.org/10.1097/01.mlr.0000185733.30697.f6

Burnett-Zeigler, I., Kim, H. M., Chiang, C., Kavanagh, J., Zivin, K., Rockefeller, K., Sirey, J. A., & Kales, H. C. (2013). The association between race and gender, treatment attitudes, and antidepressant treatment adherence. International Journal of Geriatric Psychiatry, 29(2), 169–177. https://doi.org/10.1002/gps.3984

Chand, S. P., & Arif, H. (2021). Depression. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK430847

Chauhan, N., Chakrabarti, S., & Grover, S. (2021). Identifying Poor Adherence in Outpatients with Bipolar Disorder: A Comparison of Different Measures. Journal of Neurosciences in Rural Practice, 13(01), 012–022. https://doi.org/10.1055/s-0041-1736155

Cristea, I. A., Karyotaki, E., Hollon, S. D., Cuijpers, P., & Gentili, C. (2019). Biological markers evaluated in randomized trials of psychological treatments for depression: a systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews, 101, 32–44. https://doi.org/10.1016/j.neubiorev.2019.03.022

Dell'Osso, B., Albert, U., Carrà, G., Pompili, M., Nanni, M. G., Pasquini, M., Poloni, N., Raballo, A., Sambataro, F., Serafini, G., Viganò, C., Demyttenaere, K., McIntyre, R. S., & Fiorillo, A. (2020). How to improve adherence to antidepressant treatments in patients with major depression: a psychoeducational consensus checklist. Annals of General Psychiatry, 19(1). https://doi.org/10.1186/s12991-020-00306-2

Gast, A., & Mathes, T. (2019). Medication Adherence Influencing Factors—an (updated) Overview of Systematic Reviews. Systematic Reviews, 8(1). https://doi.org/10.1186/s13643-019-1014-8

Griethuijsen, R. A. L. F., van Eijck, M. W., Haste, H., den Brok, P. J., Skinner, N. C., Mansour, N., Savran Gencer, A., & BouJaoude, S. (2014). Global Patterns in Students' Views of Science and Interest in Science. Research in Science Education, 45(4), 581–603. https://doi.org/10.1007/s11165-014-9438-6

Horne, R., Weinman, J., & Hankins, M. (1999). The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology & Health, 14(1), 1–24. https://doi.org/10.1080/08870449908407311

Interian, A. (2010). A Brief Self-Report Measure to Assess Antidepressant Adherence Among Spanish-Speaking Latinos. Journal of Clinical Psychopharmacology, 30(6), 755–757. https://doi.org/10.1097/jcp.0b013e3181fb57f8

Jimmy, B., & Jose, J. (2020). Patient Medication Adherence: Measures in Daily Practice. Oman Medical Journal, 26(3), 155–159. https://doi.org/10.5001/omj.2011.38

Krousel-Wood, M., Islam, T., Webber, L. S., Ré, R. N., Morisky, D. E., & Muntner, P. (2009). New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care. 2009, 15(1), 59–66.

Lam, W. Y., & Fresco, P. (2015). Medication Adherence Measures: An Overview. BioMed Research International, 2015(217047), 1–12. https://doi.org/10.1155/2015/217047

Lazar, J., Feng, J. H., & Hochheiser, H. (2017). Analyzing qualitative data. Research Methods in Human Computer Interaction, 299–327. https://doi.org/10.1016/b978-0-12-805390-4.00011-x

Leggett, A., Kavanagh, J., Zivin, K., Chiang, C., Kim, H. M., & Kales, H. C. (2015). The Association Between Benzodiazepine Use and Depression Outcomes in Older Veterans. Journal of Geriatric Psychiatry and Neurology, 28(4), 281–287. https://doi.org/10.1177/0891988715598227

Marasine, N. R., Sankhi, S., Lamichhane, R., Marasini, N. R., & Dangi, N. B. (2020). Self-Reported Antidepressant Drug Side Effects, Medication Adherence, and Its Associated Factors among Patients Diagnosed with Depression at the Psychiatric Hospital of Nepal. Depression Research and Treatment, 2020, 1–7. https://doi.org/10.1155/2020/7024275

McGuinness, L. A., & Higgins, J. P. T. (2020). Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Research Synthesis Methods, 12(1). https://doi.org/10.1002/jrsm.1411

Morisky, D. E., Green, L. W., & Levine, D. M. (1986). Concurrent and Predictive Validity of a Self-reported Measure of Medication Adherence. Medical Care, 24(1), 67–74. https://doi.org/10.1097/00005650-198601000-00007

Morisky, D. E., Ang, A., Krousel-Wood, M., & Ward, H. J. (2008). Predictive Validity of a Medication Adherence Measure in an Outpatient Setting. The Journal of Clinical Hypertension, 10(5), 348–354. https://doi.org/10.1111/j.1751-7176.2008.07572.x

Morisky, D. E., & DiMatteo, M. R. (2011). Improving the measurement of self-reported medication nonadherence: Response to Authors. Journal of Clinical Epidemiology, 64(3), 255–257. https://doi.org/10.1016/j.jclinepi.2010.09.002

Novick, D., Montgomery, W., Moneta, V., Peng, X., Brugnoli, R., & Haro, J. M. (2015). Antidepressant medication treatment patterns in Asian patients with major depressive disorder. Patient Preference and Adherence, 2015:9, 421–428. https://doi.org/10.2147/ppa.s68432

Ormel, J., Kessler, R. C., & Schoevers, R. (2019). Depression. Current Opinion in Psychiatry, 32(4), 348–354. https://doi.org/10.1097/yco.0000000000000505

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., & McGuinness, L. A. (2021). The PRISMA 2020 statement: an Updated Guideline for Reporting

Systematic Reviews. British Medical Journal, 372(71). https://doi.org/10.1136/bmj.n71

Rickles, N. M., Mulrooney, M., Sobieraj, D., Hernandez, A. V., Manzey, L. L., Gouveia-Pisano, J. A., Townsend, K. A., Luder, H., Cappelleri, J. C., & Possidente, C. J. (2023). A systematic review of primary care-focused, self-reported medication adherence tools. Journal of the American Pharmacists Association: JAPhA, 63(2), 477-490.e1. https://doi.org/10.1016/j.japh.2022.09.007

Rossom, R. C., Shortreed, S., Coleman, K. J., Beck, A., Waitzfelder, B. E., Stewart, C., Ahmedani, B. K., Zeber, J. E., & Simon, G. E. (2016). Antidepressant Adherence across Diverse Populations and Healthcare Settings. Depression and Anxiety, 33(8), 765–774. https://doi.org/10.1002/da.22532

Ruetsch, C., Liberman, J., Davis, T., Sajatovic, M., Velligan, D., & Forma, F. (2022). The Effect of Objectively Collected Medication Adherence Information on Bipolar I and Major Depressive Disorder Treatment Decisions: A Randomized Case Vignette Study of Psychiatric Clinicians. Journal of Affective Disorders Reports, 100344. https://doi.org/10.1016/j.jadr.2022.100344

Sansone, R. A., & Sansone, L. A. (2019). Antidepressant adherence: are patients taking their medications? Innovations in Clinical Neuroscience, 9(5-6), 41–46. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3398686/

Shiomi, M., Kurobuchi, M., Tanaka, Y., Takada, T., & Otori, K. (2021). Pill Counting in the Determination of Factors Affecting Medication Adherence in Patients with Type 2 Diabetes: A Retrospective Observational Study. Diabetes Therapy, 12. https://doi.org/10.1007/s13300-021-01091-1

Shoji, M., Maeda, H., Watanabe, F., Kazunori Tanuma, Fujiwara, A., Iwanaga, Y., Shimada, A., & Onda, M. (2023). A non-randomized, controlled, interventional study to investigate the effects of community pharmacists' cognitive behavioral therapy–based interventions on medication adherence and relevant indicators in patients with depression. BMC Psychiatry, 23(1). https://doi.org/10.1186/s12888-023-04602-5

Sirey, J. A., Banerjee, S., Marino, P., Bruce, M. L., Halkett, A., Turnwald, M., Chiang, C., Liles, B., Artis, A., Blow, F., & Kales, H. C. (2017). Adherence to Depression Treatment in Primary Care. JAMA Psychiatry, 74(11), 1129. https://doi.org/10.1001/jamapsychiatry.2017.3047

Srimongkon, P., Aslani, P., & Chen, T. F. (2019). A systematic review of measures of medication adherence in consumers with unipolar depression. Research in Social and Administrative Pharmacy, 15(1), 3–22. https://doi.org/10.1016/j.sapharm.2018.02.008

Stewart, S.-J. F., Moon, Z., & Horne, R. (2022). Medication nonadherence: health impact, prevalence, correlates, and interventions. Psychology & Health, 1–40. https://doi.org/10.1080/08870446.2022.2144923

Svarstad, B. L., Chewning, B. A., Sleath, B. L., & Claesson, C. (1999). The brief medication questionnaire: A tool for screening patient adherence and barriers to

adherence. Patient Education and Counseling, 37(2), 113–124. https://doi.org/10.1016/s0738-3991(98)00107-4

Taber, K. S. (2018). The use of cronbach's alpha when developing and reporting research instruments in science education. Research in Science Education, 48(6), 1273–1296. https://doi.org/10.1007/s11165-016-9602-2

Teeng, L. P., Guan, N. C., Kadir, M. S., & Ling, T. S. (2021). Reminder through mobile messaging application improves outpatient attendance and medication adherence among patients with depression: An open-label randomised controlled trial. Medical Journal of Malaysia, 76(5), 617–623.

Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., Dobbels, F., Fargher, E., Morrison, V., Lewek, P., Matyjaszczyk, M., Mshelia, C., Clyne, W., Aronson, J. K., & Urquhart, J. (2012). A new taxonomy for describing and defining adherence to medications. British Journal of Clinical Pharmacology, 73(5), 691–705. https://doi.org/10.1111/j.1365-2125.2012.04167.x

Warden, D., Trivedi, M. H., Carmody, T., Toups, M., Zisook, S., Lesser, I., Myers, A., Kurian, K. R. B., Morris, D., & John Rush, A. (2014). Adherence to Antidepressant Combinations and Monotherapy for Major Depressive Disorder. Journal of Psychiatric Practice, 20(2), 118–132. https://doi.org/10.1097/01.pra.0000445246.46424.fe

Wikberg, C., Westman, J., Petersson, E-L., Larsson, M. E. H., André, M., Eggertsen, R., Thorn, J., Ågren, H., & Björkelund, C. (2017). Use of a self-rating scale to monitor depression severity in recurrent GP consultations in primary care – does it really make a difference? A randomised controlled study. BMC Family Practice, 18(1). https://doi.org/10.1186/s12875-016-0578-9

Yusuf, H., Magaji, M. G., Maiha, B. B., Yakubu, S. I., Haruna, W. C., & Mohammed, S. (2021). Impact of pharmacist intervention on antidepressant medication adherence and disease severity in patients with major depressive disorder in fragile north-east Nigeria. Journal of Pharmaceutical Health Services Research, 12(2021). https://doi.org/10.1093/jphsr/rmab030