

**TJPS-49799: REVIEW**

DOI: 10.4274/tjps.galenos.2020.49799

## **Factors Associated with Antidepressant Medication Non-adherence: A review**

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05.05.2020

01.06.2020

### **ABSTRACT**

**Introduction:** Medication non-adherence is one of the major problems in treating patients with depression. Non-adherence results in an increased risk of relapse and reduced quality of life. The objective of this study was to review and summarize studies on the factors associated with antidepressant medication non-adherence in patients with depression.

**Methods:** Literature searches were performed using PubMed/Medline and Google Scholar. The search was limited to English language articles published in journals between January 2000 and December 2019. Studies that analyzed factors of non-compliance in patients with depressive disorder were included.

**Results:** Patient-related factors like forgetfulness, comorbidity, and misconception about the disease and medication, medication-related factors, polypharmacy, side effects, pill burden and cost, health care system-related factors, including physician-patient interaction, social-cultural factors like religious and cultural beliefs and stigma, and logistic factors were found to be the major factors associated with antidepressant non-adherence.

**Conclusion:** Efforts should be made to increase patient adherence by strengthening physician-patient relationships, simplifying medication regimens, and rectifying myths and beliefs held by patients with scientific information and explanations, to increase antidepressant non-adherence.

**Keywords:** adherence, antidepressants, depression, associated factors

### **INTRODUCTION**

Depression has become a major public health concern, with increased prevalence and global disease burden, due to associated mental as well as social and interpersonal disability<sup>1</sup>.

According to the World Health Organization (WHO), by 2020, it will be the second-highest known cause of worldwide disability<sup>2</sup>. It is characterized by a sad mood, pessimistic thought, lowered interest in day-to-day activities, poor concentration, insomnia or increased sleep, significant weight loss or gain, decreased energy, continuous feelings of guilt and worthlessness,

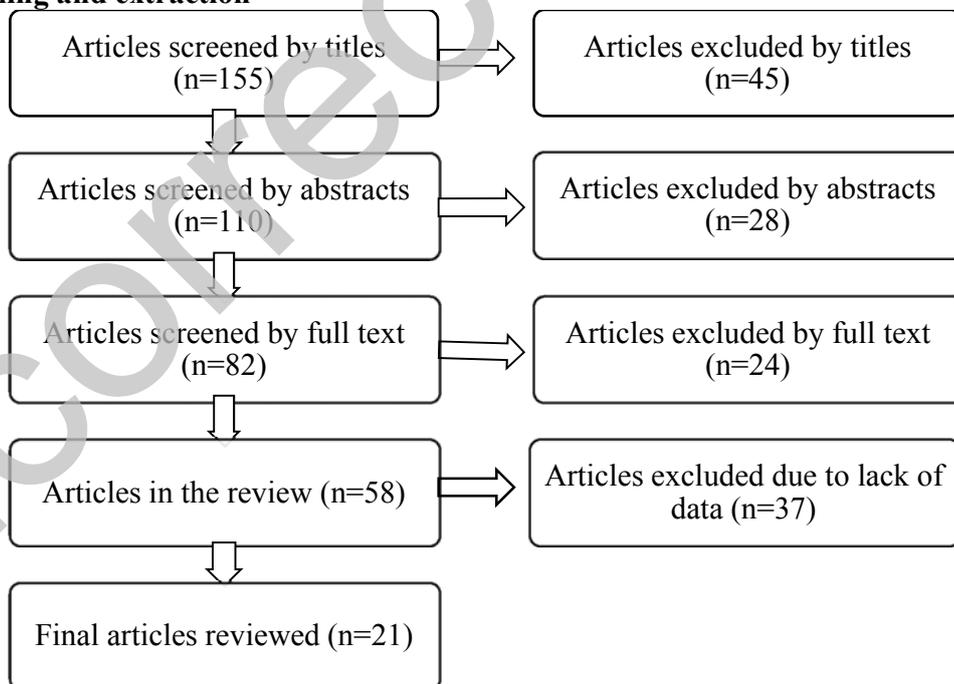
decreased libido, and suicidal thoughts occurring at least once in two weeks<sup>1,3</sup>. Antidepressant drugs are the most effective and widely used forms of treatment for depression<sup>4</sup>. Despite the availability of many effective antidepressants, 50% of patients do not achieve a complete cure of symptoms and even experience recurrence<sup>5,6</sup>. Therefore, in many patients, depression becomes a chronic disorder and may require lifelong antidepressant treatment. For the desired outcome of treatment, adherence to antidepressant medication plays a crucial role, and non-adherence is the major problem associated with antidepressant treatment. Adherence has been defined as ‘the extent to which a person’s behavior regarding taking medication, following a diet, or executing lifestyle corresponds with recommendations from a health care provider’<sup>7</sup>. The failure of patients to follow medical advice results in a risk of relapse and reduced quality of life. Many factors like patient factors, medicine related factors, health system, and social and cultural factors are associated with patients being non-adherent to prescribing antidepressants. Hence, this study was conducted to review and summarize studies about the factors associated with antidepressant medication non-adherence in patients with depression.

## METHODS

### Data Sources, Search, and Selection

A comprehensive literature review was conducted using PubMed/Medline and Google Scholar. The search was limited to English language articles published in journals between 2000 and 2019. Keywords used were: depression, depressive patients, antidepressant, antidepressant adherence, patient compliance, and discontinuation of antidepressants. We also included articles listed in the author’s reference lists and those listed in other systematic reviews. Studies were selected based on relevancy. Full articles on those studies, which deemed relevant to our study title were fully reviewed and irrelevant studies were eliminated.

### Data screening and extraction



### Study selection

For inclusion in our review, studies need to include adult or elderly patients irrespective of gender diagnosed with depression and prescribed antidepressants by physicians. Literature can be of varying methodologies i.e. observational, prospective, cross-sectional, retrospective, or survey.

Our study outcomes were the factors that caused non-adherence to antidepressants among patients with depressive disorder. Studies that did not meet our criteria were excluded during the review. Studies were discarded if they were clinical trials and reviews.

## RESULTS

One hundred and fifty-five articles were selected by title/abstract, and finally 21 were included. The total sample size was 66,148 patients. Two studies were performed in Ethiopia<sup>8, 11</sup>, one in Nepal<sup>9</sup>, Malaysia<sup>10</sup>, Island<sup>12</sup>, two in China<sup>13, 27</sup>, two in India<sup>14, 17</sup>, one in Saudi Arabia<sup>15</sup>, two in Spain<sup>16, 19</sup>, one in Italy<sup>18</sup>, three in the United States<sup>20, 23, 28</sup>, one in the UK<sup>21</sup>, one in Korea<sup>22</sup>, one in Japan<sup>24</sup>, one in Pakistan<sup>25</sup>, and one in New Zealand<sup>26</sup>. Sample sizes were less than 100 in four studies, 100–400 in fifteen studies, and more than 20,000 in two studies. Table 1 shows the main findings of these studies.

**Table 1: Study, sample, methods, and major findings of the studies.**

Study	Objective	Methodological review	Major findings
Woldekidan et al., 2019 <sup>8</sup>	To assess the level of patient satisfaction and determine associated factors with psychiatric outpatient care.	Institution-based cross-sectional study n=250 age: ≥ 18 years Structured questionnaires used to collect data.	69.2% of the participants complained of not getting sufficient information from health-care professionals working in outpatient care.
Shrestha Manandhar et al., 2017 <sup>9</sup>	To determine the medication adherence pattern in patients with depression and assess the factors associated with non-adherence.	Hospital-based prospective study n=60 age: >18 years Structured questionnaire for demographic details and medication adherence pattern.	Only 37% were adherent. The main reason for non-adherence: missed dose due to forgetfulness. Factors for non-adherence: the occupation of patients, cost of medicine, treatment duration, and the occurrence of adverse effects, the patients' perception towards disease, physician factors, and availability of medicine.
Ho et al., 2017 <sup>10</sup>	To explore the barriers and facilitators of patients' adherence to antidepressants among outpatients with MDD.	Qualitative study n=30 age: ≥18 years Semi-structured and individual in-depth interviews were conducted.	Facilitators of adherence: having insight, perceived health benefits, regular activities, patient-provider relationships, reminders, and social support networks. Barriers of adherence to antidepressants: wrong beliefs about disease or medications, forgetfulness, negative attitudes,

Abegaz et al.,2017 <sup>11</sup>	To determine the level of adherence to and clinical outcome of antidepressants and the magnitude of their ADRs.	The hospital-based prospective cross-sectional study n=217 age: ≥18 years Morisky Medication Adherence Measurement Scale-Eight (MMAS-8) was used.	lack of knowledge, and co-morbidity.  57.1% had low adherence to their medication. Weight gain was the common ADR encountered in 85.7% of patients. Adherence to medications was attributed to factors such as long-standing depression, distance from the follow-up clinic, and comorbid psychiatric illness.
Telinoiu,2016 <sup>12</sup>	To measure adherence with antidepressant medication.	Retrospective cohort study n=22,977 age: 18-75 years Health Plan Employer Data and Information Set (HEDIS), and the proportion of days covered (PDC), to measure adherence.	Adherent group: older patients aged ≥50 years, higher economic status, females, and patients having comorbid conditions like diabetes, cardiovascular, respiratory, mental health illness, and the patients who visit the hospital for follow-up.
Lu et al.,2016 <sup>13</sup>	To investigate the beliefs about antidepressant medication and associated adherence among older Chinese patients with major depression.	Cross-sectional survey n=135 age: >60 years Morisky Medication Adherence Measure (MMAM), to measure adherence.	Factors of non-adherence: forget to take the medicine, followed by when feeling better, concerns of long-term effects and addiction, and high-income respondents.
Alekhya et al., 2015 <sup>14</sup>	To study the socio-demographic factors that influence compliance with the treatment of depression.	Cross-sectional study n=103 age: >18years Questionnaire format (for socio-demographic factors)	The majority of non-adherent patients were: 21-50 years aged, males unmarried, low socio-economic status, and a high level of education.
Al Jumah et al.,2014 <sup>15</sup>	To explore patients' adherence to antidepressant medications and the factors associated with adherence.	Non-experimental cross-sectional study n=403 age: 18-60 years Used the Morisky Medication Adherence Scale (MMAS).	Females: 50.4% The average age of 39 years. Factors associated with low adherence: specific belief concerns, general harm, and overuse beliefs about antidepressant medications and younger age (<40 years).

Vives et al., 2014 <sup>16</sup>	To determine adherence level, to analyze socio-demographic factors and clinical profiles involved in adherence.	Longitudinal observational study n=29 age: ≥18 years Socio-demographic and clinical variables questionnaire, Simplified Medication Adherence Questionnaire, (SMAQ) were used.	High adherence was associated with: more follow-up visits with a psychiatrist, effective physician-patient contact, and the patient's satisfaction. Factors addressing compliance: awareness of the illness or insight, positive attitude to drugs, and tolerability (in particular regarding the side effects of medication).
Sultana et al., 2014 <sup>17</sup>	To evaluate rates and predictors of antidepressant (AD) treatment discontinuation in depressed older patients.	Population-based study n=39,557 age: ≥65 years Nationwide Italian general practice "Health Search" database (HSD) was used.	Predictors of discontinuation of antidepressants: concomitant use of >5 drugs, use of other classes of antidepressants other than SSRIs, as a result of lower tolerability.
De las Cuevas et al., 2014 <sup>18</sup>	To identify risk factors for non-adherence to antidepressant treatment	Population-based cohort study n=145 age: ≥18 years The Morisky self-report scale was used to assess adherence.	The negative attitude of patients towards their treatment increased severity of depression, and the presence and severity of side effects were associated with non-adherence.
Banerjee and Varma, 2013 <sup>19</sup>	To assess non-adherence to prescribed treatment among patients with unipolar depression.	Cross-sectional study n=239 age: 18-60 years Morisky Medication Adherence Scale (MMAS) was used.	Non-adherent patient: 66.9% Women were three times more prone to be non-adherent compared to men. Non-adherent group: women, low socioeconomic status, lack of awareness about diagnosis, and inappropriate intake of medication.
Jeon-Slaughter, 2012 <sup>20</sup>	To investigate the patients' income effect on non-adherence to selective serotonin	Population-based study n= 280 age: 18-64 years National Comorbidity	Factors leading to non-adherence: Low-income level, combined with health insurance status, African Americans than Whites,

	reuptake inhibitors (SSRIs).	Survey-Replication (NCS-R) was used.	and major depressive episode comorbidity.
Fawzi et al., 2012 <sup>21</sup>	To investigate the relationship between older depressed patients adherence to antidepressants and their beliefs and Knowledge about medication.	Population-based study n=108 age: >55 years Medication Adherence Rating Scale (MARS) and a Global Adherence Measure (GAM) was used.	Potential predictors of adherence: sociodemographic, medication, and illness variables. Older patients are more likely to adhere to medication compared to younger patients. Reasons for non-compliance: not providing sufficient knowledge about the prescribed medication.
Park et al., 2012 <sup>22</sup>	To examine factors associated with treatment-seeking in respondents with major depressive disorder.	Population census n=362 age: 18-64 years Data used from the Korean Epidemiologic Catchment Area (KECA-R) study.	Treatment-seeking by individuals with depression was affected by socio-cultural factors such as misconception and stigma of mental illness, as well as the severity of depression and comorbid conditions like anxiety, and obsessive-compulsive disorder.
Tamburrino et al., 2009 <sup>23</sup>	To survey primary care patients adherence to antidepressant medication to better understand factors associated with non-adherence.	Survey n=148 age: ≥18 years Medication Adherence Scale (MAS), and the Medical Outcome Study (MOS) were used to measure Adherence.	The majority were female. Factors for non-adherence: younger age (<40 years), careless about taking medications, worried about side effects, less satisfied with their physicians, and patient asking for a specific antidepressant to be prescribed.
Sawada et al., 2009 <sup>24</sup>	To examine persistence and compliance with antidepressant drugs.	Retrospective study n=367 age: 16-82 years Medication Possession Rate (MPR) was used.	Older people, Male, and Sertraline users were more persistent and compliant to treatment.
Taj et al., 2008 <sup>25</sup>	To elucidate predictors of non-adherence among psychiatric patients.	Questionnaire-based cross-sectional study n=128 age: ≥18 years) 19 itemed questionnaire was used.	Mean age of patients: 39.49 years. Reasons for non-adherence: comorbid condition, sedation, high medication cost, forgot to take medication, and the inability of the physicians to explain timing and dose or benefit of the medication.
Russell and Kazantzis, 2008 <sup>26</sup>	To determine medication beliefs and adherence to	Prospective study n=85 age: 18-65 years	Patients who were concerned about the need for medication and with fewer depressive symptoms

	antidepressants in primary care.	Beliefs about Medication Questionnaire (BMQ) and Medication Adherence Report Scale (MARS) were used.	were found more adherent to antidepressants.
Yeh et al., 2008 <sup>27</sup>	To determine predictors of medication adherence among patients with depression.	Cross-sectional study n=181 age: 23-61 years The self-report questionnaire used to collect data.	Predictors for adherence: treatment efficacy, the severity of depression, mental health professional-patient interaction, understanding the need to continue taking medication, social support, and patient income. Negative beliefs and perceptions decrease medication adherence. 60% discontinued treatment with an antidepressant agent.
Ashton et al., 2005 <sup>28</sup>	To identify reasons for discontinuation and noncompliance with antidepressant medications.	Survey n=344 age: 18-65 years A 42-question survey was used.	The main reason for discontinuation of treatment: having trouble in remembering to take the drug, followed by weight gain, unable to have an orgasm and, lost interest in sex.

## DISCUSSION

### a. Sociodemographic factors

From this review, it was observed that the majority of the patients who were non-adherent to their prescribed antidepressants were younger patients aged <40 years<sup>15, 21, 23</sup>. Non-adherence among younger patients could be due to having less experience with depression and associated medications. In contrast, older patients may have more experience with depressive episodes and antidepressants, which makes them more willing to complete their prescribed doses<sup>15, 23</sup>. Additionally, antidepressants are associated with common side effects like weight gain and impaired sexual function, which may be troublesome to younger patients to adhere to antidepressant drugs<sup>15, 21, 23, 29-31</sup>.

Female patients were found to be more non-adherent to prescribed antidepressants than males<sup>19, 23, 24, 32</sup>. Women play multiple roles in the family and society, such as, homemakers, spouses, mothers, professionals, and caregivers, which might cause them difficulty visiting the hospital and making them unable to adhere to their prescribed medications. However, findings contrary to these studies were reported by the work<sup>12</sup> and<sup>14</sup>, where males were more non-adherent to their regimen. This could be due to they were not permitted leave from office of they may be concerned about the deduction of payment on that particular day they took leave for visiting the hospital. Their inability to make hospital visits in their working days might have kept them away from being adhered to their treatment, 12,<sup>14, 19, 29, 33</sup>.

One of the study<sup>14</sup> showed that non-adherence and higher level of education are inversely proportional to each other. This means that when the level of education increases, adherence increases, and vice versa. Highly educated people fear about side effects and long-term effects of

the drugs, which might be due to their little knowledge about disease and drugs prescribed to them and their unwillingness to communicate with their healthcare personnel<sup>14,34</sup>.

Many studies predicted people of low socioeconomic status to be more non-adherent to antidepressants<sup>12, 14, 19, 20, 27</sup>. This could be due to unemployment or unstable income, they can't afford medicines for a long term, and frequent appointments with their physician become expensive for them, which leads to premature discontinuation and non-adherence to drug regimens<sup>27, 35</sup>. In contrast, a work<sup>13</sup> found that patients belonging to high socioeconomic status were more non-adherent to antidepressants. This could be due to higher-income people have high social status and education level. They might be more concerned about the side effects or dependence potency of antidepressants, which finally leads to decreased adherence.

#### **b. Patient-related factors**

From the literature review, patients often forgetting to take their medications was found to be a common patient-related factor for antidepressant non-adherence<sup>9, 10, 13, 25, 28, 36, 37</sup>. Also, inappropriate intake of medication or patient carelessness are the reasons for non-adherence<sup>9, 19, 23</sup>.

Patients have wrong beliefs about the disease itself or prescribed antidepressants<sup>10, 13, 15, 22, 27</sup>.

From the findings of our review, poor understanding of mental illness and medication was found to be the main barrier to depression treatment and hence adherence. Even after being diagnosed with depression, many did not consider themselves as having a mental illness. They believe they could easily overcome their mental illness on their own<sup>22, 38</sup>. They also believe that it would be resolved by having a positive thinking or complete rest without taking antidepressants<sup>3</sup>. Some people take depression as a normal part of their aging process, some even blame it as a result of their unlucky life, or weak personality rather than a mental illness<sup>39, 40</sup>.

The majority of patients taking antidepressants have misconceptions about antidepressants. They think that there is no need to take medicine in the absence of any signs or symptoms. They believe they can take less medicine or simply discontinue the medication themselves when they feel better<sup>10, 13, 41, 42</sup>.

The patient's decision on adhering to antidepressants mainly depends on the balance between necessity and concern about the safety and efficacy of prescribed medicine<sup>43, 44</sup>. So many people believe that long-term use of antidepressants is toxic and may lead to kidney damage. They are also concerned with the additive and psychological dependence potential of antidepressants, all of which affect their adherence to treatment<sup>10, 13, 15</sup>.

Patients with a positive attitude towards their disease and medication and awareness of their illness adhere more to their regimen<sup>9, 10, 16, 18, 19, 26, 27</sup>. They believe they will return to normal functioning, continuing the medications. They will communicate regularly with their physicians to enhance their knowledge about their mental illness and medication<sup>10</sup>. This all will help them cope with the response and lead to better health outcomes<sup>45</sup>.

Comorbidity, polypharmacy, and non-adherence are inter-related to each other. Comorbidity increases the number of medications be taken by patients<sup>10, 17, 25</sup>. Patients will feel pill burdens and even the economic burden since they have to take different types of medications. The complex dose schedule and the intention to save the cost may force patients to discontinue their medication, leading to non-compliance<sup>10, 20</sup>. Comorbidity also leads to logistic problems, as patients have to seek medical advice from more than one physician, getting appointments, and timely medication refills time and again<sup>25</sup>.

### **c. Medication-related factors**

It is evident from many literatures, that the majority of patients deny to continue antidepressants due to the prevalent side effects of the drug prescribed<sup>9, 11, 13, 18, 25, 26, 28</sup>. Patients mostly prefer medications that have a lower risk of weight gain, sexual dysfunction, and tiredness<sup>28</sup>.

Antidepressants are reported to cause many adverse effects like sedation, restlessness, tremor, dry mouth, decreased libido, weight gain, irregular menstrual cycles, and impotence. These unpleasant effects may impair patient quality of life and self-esteem, resulting in non-adherence to prescribed antidepressants<sup>46, 47, 48</sup>. Two of the studies<sup>17</sup> and<sup>24</sup>, patients prescribed with antidepressants other than selective serotonin reuptake inhibitors (SSRIs) were more likely to be non-adherent. This might be due to the lower side effect profile, low overdose-related cardiotoxicity, better tolerability, and overall favorable risk-benefit ratio attributed to SSRIs<sup>11, 49-52</sup>.

Adherence to treatment is greatly influenced by physician-patient interactions. One of the common reasons for non-adherence was the failure of physicians to provide adequate information on patients' illness and medications prescribed<sup>9, 15, 21, 25, 27</sup>. From the studies, the most common complaint of patients found was: physician not explaining the timing and dose of medication completely along with the benefit of therapy, and consequence of non-adherence<sup>21, 25, 46, 53</sup>. Similarly, not trusting the physician and dissatisfaction with the physician and their prescribed medication also leads to patients being non-adherent to the treatment<sup>10, 15, 23, 54, 55</sup>. Due to multiple prescribers, problems in communicating with physicians, frequent follow-up, long waiting times in hospitals, repeated medication refills, and unavailability of prescribed medications<sup>19</sup>, many patients choose to discontinue their medications<sup>9, 10</sup>. Patients lose confidence in their physician when there are multiple prescribers, which ultimately affects their medication-taking behavior. Some patients alter/stop their medication without informing their physician as they find it difficult to communicate with them. To avoid long waiting times, patients skip their appointments, leading to an insufficient amount of medication at home<sup>10</sup>.

### **d. Sociocultural factors**

Lower adherence to medication depends on the perception of the patient about his illness, which may differ by their religion and culture they belong to<sup>13, 56</sup>. A study<sup>10</sup> collected the beliefs of people from different religions and cultures. It stated that people from Malaysia believe that mental illness as a social punishment for the particular people, or as an illness of the soul caused by the weakness of the spirit. Similarly, Chinese people believe that mental illness is a symbol of lack of self-worthiness, which is measured in terms of education and monetary gain that brings honor to the family. Likewise, the Indians believe that one gets a mental illness from the evildoers<sup>57</sup>. All of these beliefs create barriers in pursuing and sticking to antidepressant regimens. Some patients want to experiment whether being prayerful will cure their depression, which forces them to stop taking the medication<sup>10, 13, 38</sup>.

Depression is still considered a social stigma. Many regard it as a sign of a personal weakness<sup>26</sup>. Regular social support and motivation from family members and co-workers help depressive patients get going their antidepressant treatment<sup>22, 27, 58</sup>. Due to fear of being stigmatized by society, many patients do not reveal their mental illness<sup>22</sup>, which influences their adherence to medication. Unsupportive family members and co-workers also discourage patients from continuing their medication<sup>10</sup>, which further makes their mental illness severe.

### **e. Logistic factor**

Many patients who live far from city areas or hospitals have poor access to healthcare facilities and hence hinder patients from adhering to antidepressants<sup>9-11</sup>.

## CONCLUSION

From our review, we conclude that patient-related factors like forgetfulness, comorbidity, and misconception about the disease and medication, medication-related factors, polypharmacy, side-effects, pill burden and cost, healthcare-system related factors, including physician-patient interaction, sociocultural factors like religious and cultural beliefs and stigma, and logistic factors are the major barriers to antidepressant adherence. Hence, efforts should be made to increase patient adherence by strengthening physician-patient relationships. Physicians should emphasize patient education that includes an explanation of drug, dose, duration, and timing of administration, possible side effects, adverse effects, lag time before the onset of treatment and relief of symptoms, and consequence of non-adherence. In the case of comorbid conditions, physicians should make the medication regimen simple. Additionally, they should focus on rectifying the myths and beliefs held by patients with scientific information and explanations.

## CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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