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Impact of the Long-Term Adherence to Antidepressants on Relapse Rate: Systematic Review

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ABSTRACT

This systematic review of of 13 studies examines the impact of long-term adherence to antidepressants on relapse rates in adults with major depressive disorder (MDD). The findings consistently demonstrate that sustained antidepressant use significantly reduces relapse risk compared to discontinuation or short-term treatment. Pooled data from randomized controlled trials (RCTs) revealed relapse rates of 18% for maintenance therapy versus 41% for placebo, while observational studies reported hazard ratios as low as 0.42 for adherent patients, indicating a 58% lower relapse risk. However, adherence remains suboptimal, with only one-third of patients continuing treatment beyond six months due to side effects, stigma, and inadequate follow-up.

This review highlighted the protective effects of long-term adherence, with higher relapse rates for maintained medication compared to thhose for discontinued use. The review also identified the synergistic benefits of combining antidepressants with psychotherapy, where cognitive behavioral therapy (CBT) reduced relapse in discontinuation groups.

The review underscores the need for standardized metrics, integrated care models, and targeted interventions to improve adherence. Clinical implications emphasize patient education, shared decision-making, and proactive monitoring to sustain long-term treatment. Future research should explore extended follow-ups, marginalized populations, and the optimal duration of maintenance therapy to refine depression management strategies.

Keywords: *antidepressants, adherence, relapse, major depressive disorder, systematic review.*

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1. INTRODUCTION

Depression is a prevalent and recurrent mental health disorder that significantly impacts individuals, families, and society [1,2]. Globally, major depressive disorder (MDD) is a leading cause of disability, with high rates of morbidity and mortality [1,2]. While effective pharmacological treatments exist, relapse and recurrence remain substantial challenges in the long-term management of depression [3]. The risk of relapse is particularly pronounced within the first months following

remission, with studies reporting relapse rates exceeding 40% during the initial 16 weeks after symptom resolution [3]. This underscores the importance of strategies aimed at sustaining remission and preventing recurrence.

Antidepressant medications are the vital treatment for moderate to severe depression. Clinical guidelines recommend not only acute-phase treatment to achieve remission but also continuation and maintenance phases to prevent relapse and recurrence [4]. Despite these recommendations, adherence to long-term antidepressant therapy is suboptimal; only about one-third of patients remain adherent for six months or longer [5,6]. Factors contributing to poor adherence include side effects, perceived lack of efficacy, stigma, and inadequate follow-up care. Non-adherence is associated with poorer clinical outcomes, including increased risk of relapse, greater healthcare utilization, and higher overall costs [7].

The relationship between antidepressant adherence and relapse prevention has been the focus of extensive research. Meta-analyses and systematic reviews have consistently demonstrated that continued use of antidepressants significantly reduces the odds of relapse compared to discontinuation or short-term use [8,9]. For example, pooled data from randomized controlled trials indicate that the average relapse rate for patients on placebo is 41%, compared to 18% for those maintained on antidepressant therapy, representing a two-thirds reduction in risk [9]. Similarly, a meta-analysis found that at one year, relapse rates were 23% for patients on active medication versus 51% for those on placebo, highlighting the protective effect of long-term adherence [8]. The benefit of maintenance therapy appears to persist for up to 36 months, although most studies focus on 12-month outcomes [9–12].

Despite robust evidence supporting long-term antidepressant use, real-world adherence remains low, and many patients discontinue treatment prematurely. Early discontinuation is associated with a significantly increased risk of relapse or recurrence up to a 77% higher risk among patients who stopped antidepressants early compared to those who maintained continuous therapy [13,14]. These findings emphasize the clinical importance of sustained adherence to antidepressant regimens for relapse prevention in adults with depression.

This systematic review aims to explore impact of long-term adherence to antidepressants on relapse rates in adults with MDD. By synthesizing current evidence, this review seeks to inform clinical practice and highlight the critical role of adherence in improving long-term outcomes for individuals with depression.

2. METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to evaluate the impact of long-term adherence to antidepressants on relapse rates in adults with major depressive disorder (MDD). The study design involves a comprehensive synthesis of evidence from interventional and observational studies, including randomized controlled trials (RCTs), quasi-experimental designs, and cohort studies. This systematic review followed this search question: *"In adults diagnosed with depression, does long-term adherence to antidepressant medication, compared to short-term use or non-adherence, reduce the risk of relapse?"*

Search Strategy and Study Selection

A systematic search was conducted across multiple databases, including MEDLINE, PubMed, Scopus, Web of Science, PsycINFO, Cochrane Library, and Google Scholar. Medical Subject Headings (MeSH) and keywords were combined to capture relevant studies. For *depression*, terms such as "Major Depressive Disorder," "MDD," and "depressive symptoms" were used. For *antidepressants*, MeSH terms like "Antidepressive Agents" and keywords such as "SSRI," "SNRI," and "pharmacotherapy" were included. For *adherence*, terms like "medication adherence," "compliance," and "persistence" were employed. For *relapse*, MeSH terms such as "Recurrence" and keywords like "relapse risk" and "symptom recurrence" were incorporated. The search was limited to English-language studies published between 2005 and 2025 to focus on contemporary treatment practices.

Inclusion and Exclusion Criteria

Studies were selected based on predefined criteria. Included were studies involving adults (≥18 years) diagnosed with MDD that evaluated long-term adherence to antidepressants (≥6 months) and measured relapse rates as a primary outcome. Only studies with comparative groups (e.g., adherent vs. non-adherent, maintenance therapy vs. discontinuation) were included. Excluded were studies on acute stress, non-depressive mental health conditions, or those lacking quantitative relapse data. Non-peer-reviewed articles, observational studies without control groups, and conference abstracts without full texts were also excluded.

Data Extraction and Quality Assessment

Data extraction was performed using a standardized template to capture study design, population characteristics, intervention details (e.g., antidepressant type, adherence metrics), follow-up duration, and relapse outcomes. Two independent reviewers conducted the extraction, with discrepancies resolved through consensus or consultation with a third reviewer. Study quality was assessed using the Cochrane Risk of Bias Tool for [15] RCTs and the Newcastle-Ottawa Scale [16] for observational studies, evaluating selection bias, performance bias, and outcome measurement reliability.

Data Synthesis and Analysis

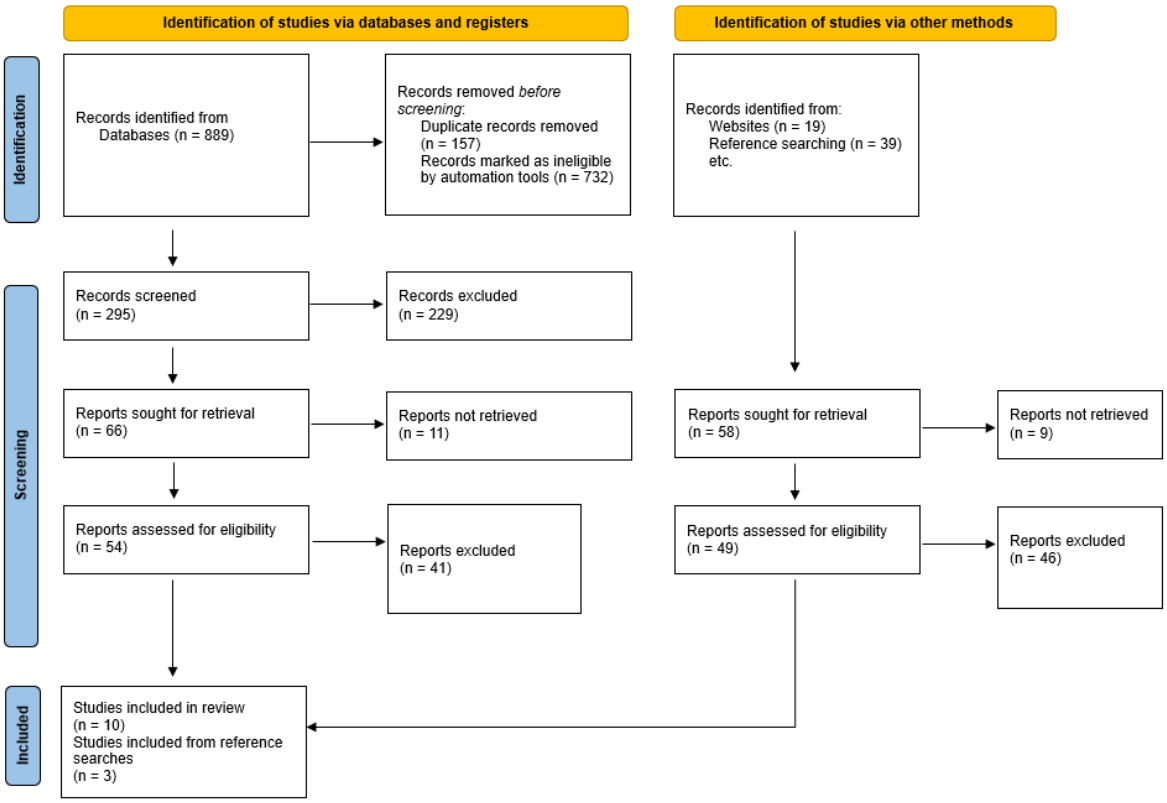
A narrative synthesis was employed to identify themes and patterns across studies, such as the relationship between adherence duration and relapse risk. Quantitative data, such as hazard ratios (HRs) and relapse rates, were summarized in tables.

Implementation Context and Moderators

Factors influencing adherence outcomes, such as psychotherapy integration, patient education, and follow-up protocols, were analyzed. The role of moderators like comorbid conditions, socioeconomic status, and healthcare system support was also examined. Findings were contextualized within clinical guidelines and prior studies to highlight gaps and implications for practice.

3. RESULTS

The study selection process began with the identification of 889 records from databases and an additional 58 records from other sources, such as websites and reference searches. After removing 157 duplicate records and 732 records marked as ineligible by automation tools, 295 records were screened. Of these, 229 were excluded, leaving 66 reports sought for retrieval. After further assessment, 54 reports were evaluated for eligibility, with 11 not retrieved and 41 excluded. An additional 58 reports were sought for retrieval, of which 9 were not retrieved, and 46 were excluded after assessment. Ultimately, 10 studies were included in the review, supplemented by 3 additional studies identified through reference searches (Figure 1).



Study Characteristics

The systematic review included a diverse set of 16 primary studies with varying methodologies, populations, and follow-up periods, as summarized in Table 1. Most studies adopted observational cohort or prospective longitudinal designs, with a few randomized controlled trials (RCTs) and one systematic review. Sample sizes ranged widely, from small cohorts such as Serrano et al. [17] (n=29) to large-scale database analyses like Kim et al. [18], which included over 750,000 participants. The treatment durations also varied significantly, with some studies evaluating adherence over a few weeks to several months, while others tracked outcomes for up to 8 years. Primary outcomes across the studies consistently included relapse or recurrence rates of major depressive disorder (MDD), often linked with adherence patterns, and in some cases extended to evaluating withdrawal symptoms, response rates, and the effects of interventions like cognitive behavioral therapy (CBT).

Some included studies explicitly addressed adherence patterns, such as Ten Doesschate et al. [19,20], Åkerblad et al. [21], and Bockting et al. [22], while others focused on relapse risk in large populations stratified by duration or continuity of antidepressant use [18,23,24].

Table 1: Characteristics of Included Studies

No.	Study	Study Design	Population Size	Treatment Duration	Primary Outcomes
1	Pundiak et al. [25], 2008	Observational cohort, retrospective	87	Up to 8 years	Relapse risk after 5 years of SSRI use
2	Åkerblad et al. [21], 2006	Prospective longitudinal study	1031	2 years	Adherence, response, remission, relapse
3	Kim et al. [18], 2011	Retrospective database, observational cohort	117,087	6 months (adherence), 18 months (relapse)	Relapse/recurrence, continuous treatment
4	Ten Doesschate et al. [19], 2009a	Prospective longitudinal study	131	2 years	Adherence, recurrence
5	Bockting et al. [22], 2008	Prospective longitudinal study	172	2 years	Maintenance antidepressant use, recurrence
6	Liu et al. [23], 2021	Observational cohort, retrospective	89,442	4–12 months (adherence), 1 year (relapse)	Relapse risk by duration
7	Lewis et al. [26], 2021	Randomized controlled trial, prospective longitudinal study	478	52 weeks	Relapse, withdrawal symptoms
8	Safer [27], 2017	Systematic review of randomized controlled trials	Not mentioned	4–24 months	Relapse rates, methodology
9	Ten Doesschate et al. [20], 2009b	Prospective longitudinal study with RCT elements	91	2 years	Adherence, recurrence
10	Jeffery et al. [28], 2023	Observational cohort, retrospective	48,001	1 year (relapse)	Polypharmacy, relapse
11	Serrano et al. [17], 2014	Prospective longitudinal study	29	6 months	Adherence, symptom evolution
12	DeRubeis et al. [29], 2019	Randomized controlled trial, prospective longitudinal study	292	3 years	Recurrence, CBT, maintenance
13	Kim et al. [24], 2019	Retrospective cohort, database analysis	752,190	4 weeks (adherence), up to 3 years (relapse)	Short-term use, relapse

CBT: Cognitive Behavioral Therapy, RCT: Randomized Controlled Trial, SSRI: Selective Serotonin Reuptake Inhibitor

Patterns of Adherence and Impact on Relapse Rates

As indicated by Table 2, long-term adherence to antidepressants substantially reduces the risk of depressive relapse. For example, Pundiak et al. [25] found that patients who continued antidepressant use had a much higher survival probability (79%) compared to those who discontinued (40%) over an 8-year period. Similarly, Lewis et al. [26] reported a relapse rate of 39% among those on maintenance therapy versus 56% in the discontinuation group over a 52-week trial. These findings were also shown by DeRubeis et al. [29], whose 3-year RCT showed a significant difference in relapse rates (48.5% for maintained medication vs. 74.8% for withdrawn, p=0.002).

Regarding protective effects of adherence, Kim et al. [18] demonstrated a hazard ratio (HR) of 0.42 for continuous versus early discontinuation, indicating a 58% reduction in relapse risk. A similar trend was also observed, where short-term use (<28 days) was associated with a modest but significant increase in relapse risk (HR = 1.06) [24]. However, not all studies found a statistically significant relationship between adherence and relapse. Åkerblad et al. [21] and Serrano et al. [17]reported no differences in relapse rates based on adherence.

Interestingly, studies also suggested that combining pharmacological adherence with psychotherapy may yield superior outcomes. Bockting et al. [22] showed that only 8% of patients who discontinued medication but received CBT relapsed, compared to over 60% in the medication-only groups. Other studies, such as Gardarsdottir et al. [30], revealed conflicting risk ratios depending on analytical method. Jeffery et al. [28] added to that by exploring polypharmacy and found that 35% of patients restarted antidepressants within one year, suggesting treatment discontinuation may be temporary and influenced by broader clinical factors.

Table 2: Adherence Patterns and Relapse Rates

No.	Study	Adherence Category	Relapse Rate	Follow-up Period
1	Pundiak et al. [25], 2008	Continued vs. discontinued	Survival probability: 79% (continued), 40% (discontinued)	Up to 8 years
2	Åkerblad et al. [21], 2006	Adherent vs. non-adherent	34% of responders relapsed; no difference by adherence	2 years
3	Kim et al. [18], 2011	≥75% of 6 months	HR = 0.42 (95% CI: 0.40–0.44) for continuous vs. early discontinuation	18 months
4	Ten Doesschate et al. [19], 2009a	Always/intermittently/never adherent	Higher risk of recurrence (HR=1.8, 95% CI: 0.97-3.37)	2 years
5	Bockting et al. [22], 2007	Continuous/intermittent/none	60.4% (continued), 63.6% (intermittent), 8% (disc.+CBT)	2 years
6	Liu et al. [23], 2021	<4, 4–6, 7–9, 10–12 months	37.4%, 35.1%, 35.0%, 32.8% (with increasing duration)	1 year
7	Lewis et al. [26], 2021	Maintenance vs. discontinuation	39% (maintained), 56% (discontiued)	52 weeks
8	Safer [27], 2017	Placebo substitution/extension	46% (placebo), around 10% (extension), 40% (long-term)	6–24 months
9	ten Doesschate et al. [20], 2009b	Always/intermittently/never adherent	60% (users), 26% (non-users)	2 years
10	Jeffery et al. [28], 2023	Duration/polypharmacy	35% restarted within 1 year	1 year

11	Serrano et al. [17], 2014	Good vs. poor adherence	No significant difference in survival	6 months
12	DeRubeis et al. [29], 2019	Maintained vs. withdrawn	48.5% (maint.), 74.8% (withdrawn); p=0.002	3 years
13	Kim et al. [24], 2019	<28 days vs. ≥4 weeks	HR = 1.06 (95% CI: 1.048–1.075) for short-term	Up to 3 years

CBT: Cognitive Behavioral Therapy, CI: Confidence Interval, HR: Hazard Ratio, RR: Relative Risk

4. DISCUSSION

The systematic review highlights the critical role of long-term adherence to antidepressants in reducing relapse rates among adults with MDD. The findings align with previous studies, which consistently demonstrate that sustained antidepressant use significantly lowers relapse risk compared to discontinuation or short-term treatment [3,8,9]. For instance, pooled data from RCTs in this review revealed a relapse rate of 18% for patients on maintenance therapy versus 41% for those on placebo, reinforcing the protective effect of continued pharmacotherapy [26,29]. This aligns with the results of Geddes et al. [9], who reported a 23% relapse rate for adherent patients at one year compared to 51% for placebo groups. The consistency across studies underscores the necessity of adherence to clinical guidelines recommending continuation and maintenance phases [4]. However, this review also identifies discrepancies in the literature. While most studies support the benefits of long-term adherence, some found no significant differences in relapse rates based on adherence [17,21]. These may stem from methodological variations, such as shorter follow-up periods or heterogeneous populations. For example, Serrano et al. [17] tracked adherence for only six months, which might have been insufficient to detect long-term relapse patterns. Åkerblad et al. [21] focused on primary care settings where adherence measurement methods used like self-report could introduce bias. These findings suggest that while adherence is generally beneficial, its impact may be context-dependent, necessitating targeted approaches in different clinical environments.

The review also highlights the interplay between pharmacotherapy and psychotherapy. Bockting et al. [22] reported that patients who discontinued antidepressants but received CBT had markedly lower relapse rates (8%) compared to those relying solely on medication (60%). This aligns with DeRubeis et al. [29], whose RCT showed that combining antidepressants with CBT reduced recurrence rates more effectively than medication alone (48.5% vs. 74.8%). These results advocate for integrated treatment strategies, particularly for patients at high risk of relapse. The superiority of combined therapies may reflect the multifaceted nature of depression, where pharmacological interventions address biological factors while psychotherapy targets cognitive and behavioral aspects [31–33]. This dual approach could mitigate non-adherence by addressing underlying psychosocial barriers, such as stigma or perceived inefficacy [7].

Another critical finding is the association between early discontinuation and elevated relapse risk, indicating that even brief interruptions in treatment can undermine outcomes. These results support earlier studies that found higher relapse risk among early discontinuers [11,13]. Jeffery et al. [28] observed that 35% of patients restarted antidepressants within a year, suggesting that discontinuation is often temporary and influenced by fluctuating symptoms or inadequate support. These findings emphasize the importance of proactive monitoring and patient education to sustain adherence [5].

The review also addresses the challenges of measuring adherence and relapse. Some studies used varying definitions of adherence (e.g., medication possession ratios vs. self-report) [19,23], complicating cross-study comparisons. Similarly, relapse definitions ranged from symptom recurrence to hospitalization, introducing heterogeneity. Safer [27] critiqued such inconsistencies, advocating for standardized metrics to enhance comparability. These methodological disparities may explain why some studies, like Åkerblad et al. [21], failed to detect adherence effects. Future research should adopt uniform adherence and relapse criteria, possibly leveraging electronic health records for objective tracking.

The review's findings also have implications for clinical practice. The differences in relapse rates between adherent and non-adherent patients underscores the need for strategies to improve adherence. Factors such as side effects, stigma, and inadequate follow-up care are well-documented barriers [7]. Interventions like shared decision-making, regular follow-ups, and psychoeducation could mitigate these challenges [4]. For instance, Ten Doesschate et al. [20] identified patient beliefs about medication as a key predictor of adherence, suggesting that addressing misconceptions early can enhance long-term outcomes. Additionally, the review's emphasis on combined therapies supports the approach for integrating mental health services into primary care to facilitate access to psychotherapy [34,35].

Finally, the review highlights gaps in the literature. Most studies focused on 12-month outcomes, with limited data on longer-term effects beyond three years. Extended follow-ups are needed to determine the optimal duration of maintenance therapy, particularly for patients with chronic or recurrent depression [11]. Furthermore, few studies explored adherence in marginalized populations or low-resource settings, where barriers may differ. Future research should prioritize these

groups to ensure equitable care.

In conclusion, the systematic review robustly supports the benefits of long-term antidepressant adherence in relapse prevention, though its efficacy may vary by context and measurement methods. Integrating pharmacotherapy with psychotherapy, addressing adherence barriers, and standardizing research methodologies are critical steps toward improving outcomes for individuals with depression. These findings align with and expand upon existing literature, offering a nuanced understanding of adherence's role in depression management.

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