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# Adherence to immunosuppressive medications in solid organ transplant recipients: a narrative review of influencing factors

## Przestrzeganie zaleceń dotyczących przyjmowania leków immunosupresyjnych przez biorców przeszczepów narządów litych: przegląd opisowy czynników mających na to wpływ

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A – Development of the concept and methodology of the study/Opracowanie koncepcji i metodologii badań; B – Query - a review and analysis of the literature/Kwerenda – przegląd i analiza literatury przedmiotu; C – Submission of the application to the appropriate Bioethics Committee/Złożenie wniosku do właściwej Komisji Biotycznej; D – Collection of research material/Gromadzenie materiału badawczego; E – Analysis of the research material/Analiza materiału badawczego; F – Preparation of draft version of manuscript/Przygotowanie roboczej wersji artykułu; G – Critical analysis of manuscript draft version/Analiza krytyczna roboczej wersji artykułu; H – Statistical analysis of the research material/Analiza statystyczna materiału badawczego; I – Interpretation of the performed statistical analysis/Interpretacja dokonanej analizy statystycznej; K – Technical preparation of manuscript in accordance with the journal regulations/Opracowanie techniczne artykułu zgodne z regulaminem czasopisma; L – Supervision of the research and preparation of the manuscript/Nadzór nad przebiegiem badań i przygotowaniem artykułu

STRESZCZENIE

**PRZESTRZEGANIE ZALECEŃ DOTYCZĄCYCH PRZYJMOWANIA LEKÓW IMMUNOSUPRESYJNYCH PRZEZ BIORCÓW PRZESZCZEPÓW NARZĄDÓW LITYCH: PRZEGLĄD OPISOWY CZYNNIKÓW MAJĄCYCH NA TO WPŁYW**

**Cel pracy.** Celem niniejszego przeglądu było dokonanie oceny przestrzegania zaleceń do leczenia immunosupresyjnego oraz identyfikacja czynników je determinujących. Analiza wcześniejszych doniesień pozwoliła na sformułowanie rekomendacji dotyczących kierunków interwencji oraz metod wspierania przestrzegania zaleceń w populacji biorców przeszczepów.

**Materiał i metody.** Strategia wyszukiwania opierała się na przeglądzie literatury dostępnej w bazie PubMed, obejmującym publikacje z lat 1995-2023. Zastosowano następujące hasła MeSH: 'Adherence', 'Compliance' lub 'Persistence' oraz 'Immunosuppressive medications'; 'Solid organ transplant recipients'. Do przeglądu kwalifikowano artykuły zgodne z określonymi celami badania.

**Wyniki.** W wyniku przeglądu literatury zidentyfikowano 99 publikacji, z których po selekcji odrzucono 29, a do dalszej analizy włączono 70. W kolejnym etapie, po konsultacjach zespołu ekspertów, wykluczono 37 prac, pozostawiając 33 publikacje włączone do przeglądu. Analizowane badania w większości dotyczyły dorosłych biorców przeszczepu nerki, obejmując okres obserwacji do 5 lat po transplantacji.

**Wnioski.** Przestrzeganie zaleceń do leczenia immunosupresyjnego jest złożonym, wieloczynnikowym procesem, na który wpływają czynniki socjodemograficzne, psychologiczne, związane z terapią, systemem ochrony zdrowia oraz kulturowe. Zarówno intencjonalny, jak i nieintencjonalny brak przestrzegania zaleceń pozostają istotnym wyzwaniem, szczególnie w grupach wysokiego ryzyka, takich jak młodzież. Skuteczne strategie powinny łączyć uproszczone schematy leczenia, edukację, wsparcie psychospołeczne oraz rozwiązania systemowe. Integracja tych działań w rutynowej opiece pacjentów po przeszczepieniu może poprawić przestrzeganie zaleceń i dawać długoterminowe efekty, a przyszłe badania powinny uwzględniać rolę czynników społecznych w przestrzeganiu zaleceń uwzględniając standaryzowane metody badań.

Słowa kluczowe: adherencja, immunosupresja, czynniki determinujące, biorcy przeszczepów narządowych

ABSTRACT

**ADHERENCE TO IMMUNOSUPPRESSIVE MEDICATIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS: A NARRATIVE REVIEW OF INFLUENCING FACTORS**

**Aim.** This review aimed to assess immunosuppressive medication adherence and to identify influencing factors. The analysis of prior studies allowed for the formulation of recommendations concerning intervention strategies and methods to support adherence in transplant recipients.

**Material and methods.** The search strategy was based on literature review of articles published from 1995 to 2023 in the PubMed. The following Medical Subject Headings (MeSH) terms were used: 'Adherence' or 'Compliance' or 'Persistence'; 'Immunosuppressive medications'; 'Solid organ transplant recipients'. Articles were considered for review if they aligned with the specified objectives.

**Results.** A meticulous literature search yielded 99 titles, with 29 manuscripts were eliminated and 70 were selected for analysis. Following consensus, 37 were excluded, leaving 33 manuscripts for review. The analysis highlighted a predominant focus on kidney transplant recipients among adults. Post-transplant periods varied up to 5 years.

**Conclusions.** Adherence to immunosuppressive therapy is a complex, multifactorial process shaped by sociodemographic, psychological, therapy-related, healthcare system, and cultural factors. Both intentional and unintentional non-adherence remain significant challenges, particularly among high-risk groups such as adolescents. Effective strategies should combine simplified regimens, tailored education, psychosocial support and system-level solutions. Integrating these approaches into routine post-transplant care may enhance adherence and improve long-term outcomes, while future research should address the role of social determinants using standardized methodologies.

**Key words:** adherence, immunosuppressive medications, influencing factors, solid organ transplant recipients

## INTRODUCTION

In the context of healthcare and medicine, adherence refers to a patient's ability and willingness to follow a prescribed treatment plan or medical regimen as recommended by a healthcare provider. According to the Ascertaining Barriers for Compliance (ABC) taxonomy, adherence to a medication regimen involves patients taking their medications as prescribed. This adherence process is characterized by three interrelated phases: initiation, implementation, and continuation or discontinuation [1]. Initiation occurs when the patient takes the first dose of a prescribed medication. Implementation is the extent to which the patient's actual dosing is consistent with the prescribed dosing regimen, which spans the period from initiation to the last dose. Implementation involves two key aspects: taking the medication (as prescribed versus skipped, extra or reduced dose) and timing (as prescribed versus late or early). In the context of non-adherence, discontinuation takes place when the patient ceases to take the prescribed medication against the clinician's advice [2]. Solid organ transplantation is the preferred treatment for patients with organ failure, as it is cost-effective and improves both patient survival and their quality of life. Transplant recipients are placed on life-long regimen of immunosuppressive medications, and adherence to these medications is crucial for the effectiveness of the treatment [3]. Non-adherence to immunosuppressive therapy results in a higher rate of acute or chronic rejection, leading to a loss of graft function and contributing to an increase in the economic burden on the healthcare system [4]. Non-adherence to immunosuppressive medications is the third cause of graft loss following rejection and systemic infections [5]. Research identified numerous factors which influence adherence to immunosuppressive therapy among patients after organ transplantation, which can be divided into several main groups. These encompass sociodemographic factors, individual-related factors, condition-related factors, therapy-related factors, and health care system factors [3]. A review of previous reports on immunosuppressive treatment adherence, an understanding of the influencing mechanisms, and an assessment of the effectiveness of prior adherence improvement methods will help us establish guidelines for creating effective strategies to improve patient adherence following organ transplantation.

## AIM

The primary objective of this review was to assess the level of adherence to immunosuppressive medications among solid organ transplant recipients and to identify factors influencing this adherence.

## MATERIALS AND METHODS

Systematic reviews are most often associated with meta-analysis. However, reviews of qualitative information can also be conducted with the same level of rigor, transparency, and replicability. Within this approach, two main methods are distinguished: narrative review and meta-synthesis. In this study, a narrative review was chosen as it is particularly suitable when analyzing a collection of quantitative studies that apply diverse methodologies and theoretical frameworks. This method allows for the synthesis of findings without focusing on statistical significance, enabling broader interpretation of the available evidence. Moreover, a narrative review provides a useful means of linking together studies on different aspects of a topic, supporting reinterpretation, integration of knowledge, and the development or refinement of theoretical perspectives [6].

The search strategy was based on literature search of articles published from 1995 to 2023 in the PubMed. The following Medical Subject Headings (MeSH) were used:

- 'Adherence' or 'Compliance' or 'Persistence'
- 'Immunosuppressive medications'
- 'Solid organ transplant recipients'

The search strategy aimed to retrieve all relevant studies using a conventional review approach. Articles were considered for review if they aligned with the specified objectives. The selection criteria included the following:

- inclusion of a study population comprising of patients after transplantation,
- measurement of the level of adherence to immunosuppressive medications,
- provision of information on barriers affecting adherence to immunosuppressive medications,
- provision of information on methods to improve patient adherence.

Letters to the editor, books, conference proceedings and papers validating methods used to assess adherence were excluded from the evaluation. Articles in languages other than English or Polish were also excluded. Manuscripts that met the inclusion criteria were collected, analyzed, and interpreted, while those not meeting the specified criteria were omitted. Two independent reviewers assessed each article based on the inclusion criteria. The review team evaluated articles on adherence to immunosuppressive therapy, considering aspects such as the level

of adherence, factors influencing adherence, and methods to assess and improve patients' adherence. After reaching consensus on the inclusion criteria for identified articles, full texts were obtained for review. Any disagreements between reviewers regarding article selection were resolved during a consensus meeting with a third reviewer. The flow diagram illustrating the study selection process is presented in Fig. 1.

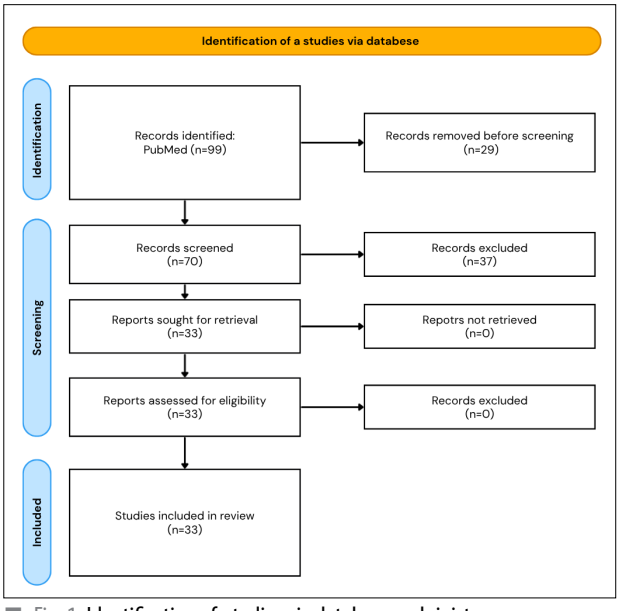


Fig. 1. Identification of studies via databese and rigisters

## RESULTS

Following a thorough literature search, each reviewer identified a total of 99 articles. The reviewers eliminated 29 manuscripts, and after a consensus meeting, 70 manuscripts were selected for abstract analysis. Subsequently, 37 manuscripts were excluded during this analysis, resulting in the identification of 33 manuscripts for inclusion in this review.

The analysis of the included manuscripts revealed that the most common population described in research on adherence to immunosuppressive medications comprised of adults who had undergone a kidney transplant. Additionally, manuscripts included in the review focused on patients after heart, liver, or lung transplantation. The post-transplantation period in the inclusion criteria varied among the studies, ranging from immediately after transplantation unt up to 5 years.

### Adherence to immunosuppressive medications and types of non-adherence

Despite the acknowledged necessity of taking medication among organ transplant recipients, a subset of patients exhibits non-adherence. According to various references, the non-adherence rate among adults ranged from 6% to as much as 90%, as assessed through different methods such as questionnaires, blood serum drug levels, or microelectronic event monitoring [3,4,7-10]. The estimated prevalence of non-adherence among pediatric patients was approximately 30% [11]. Among the studies included in this review, adherence was assessed across various types of solid organ transplant recipients, notably, kidney transplant recipients were the most frequently represented group, with a total of 24 identified studies. Based on the aggregated evidence, the reported rates of non-adherence ranged from 5.9% to 89.2% [3,4,7-9,11-29]. Among heart transplant recipients, non-adherence rates ranged from 34% to 64% [10,30-31], among liver recipients from 56% to 68% [21,32], and among lung recipients from 34% to 41% [30,33-34]. It should be noted, however, that the studies included in the review employed heterogeneous methodologies for assessing adherence, which may account for the observed variability in the reported rates. Recent reports have categorized adherence to immunosuppressive drugs as intentional and unintentional. Intentional non-adherence occurs when patients deliberately alter their medication regimens against medical advice. According to the literature, the most prevalent intentional lapse was related to taking less medication than prescribed [3,12]. The causes of unintentional non-adherence often included forgetfulness, especially in situations outside normal routines or when the medical regimen was changed, financial problems or the unavailability of medications [7].Reasons for intentional non-adherence include concerns about the regimen and not refilling prescriptions, leading to adjusting doses to ensure daily intake until the next refill, which was connected with other factors influencing adherence [12].

### Factors influencing adherence to immunosuppressive medications

Factors influencing adherence to immunosuppressive medications in patients after organ transplantation can be categorized into several main groups. These include sociodemographic factors, individual-related factors (personal), condition-related factors (clinical patient characteristics), therapy-related factors (treatment factors) and healthcare system factors. Additionally, some authors identified cultural factors in their research, placing them outside the sociodemographic or personal categories.

### Sociodemographic factors

As regards the sociodemographic factors that negatively influenced adherence to immunosuppressive medications, researchers identified characteristics such as younger age, higher education, employment status, marital status [8,12-16,32,35], and higher family income [11].

The observation that younger age increased the risk of non-adherence was substantiated by numerous authors and predictive models. Conversely, older patients were found to encounter challenges, including comorbidities, physical limitations, and social isolation, which might result in two divergent outcomes: either non-adherence or heightened awareness of their limitations, leading to increased diligence in adhering to prescribed drug regimens and medical follow-up [17]. While younger age is a significant predictor of low adherence in adults, this factor must be interpreted with caution when applied to pediatric patients. As regards the pediatric population, adolescents are more non-adherent than younger children. The

process of maturation introduces changes that may increase the likelihood of adolescents neglecting or rejecting medication treatment [11,30]. In the pediatric population, stability in a multiparent home environment was found to have a positive influence on adherence [30]. This finding stayed in line with observations concerning adults, where social support was closely associated with health literacy. Previous evidence in solid organ transplantation indicated that practical, emotional, and overall social support was correlated with improved adherence [31]. Marital status was also identified as a predictive factor for adherence [16,17]. Unmarried recipients, whether single, divorced, or widowed were found to be at a higher risk of medication non-adherence post-transplantation, potentially attributable to the absence of family-based supervision [17].

Surprisingly, higher education negatively influenced adherence to immunosuppressive medication [8]. Possessing a university degree was associated with higher rates of intentional non-adherence. This might be explained by the notion that individuals with higher education could feel equipped with skills to recognize and weigh up the benefits and risks of immunosuppressive medication. It strongly suggests that intentional non-adherence did not stem from the lack of understanding or health literacy [36]. Conversely, the lack of knowledge about the usefulness of immunosuppressive medications was linked to medication non-adherence. This implies a need for educational interventions aiming to improve the attitudes and knowledge of patients [8].

According to higher income, it had a negative influence on adherence, particularly among populations in countries with free access to immunosuppressive medications. Patients with a lower socioeconomic status, who were granted improved access to post-transplant healthcare, including immunosuppressive medications, appeared to place greater value on their regained health, which translated into better adherence. In contrast, higher socioeconomic status was associated with poorer adherence, possibly because individuals with greater financial resources already had broader access to healthcare in general and to post-transplant care, which may have reduced their sense of vulnerability and led to less consistent treatment adherence [11,18]. This observation did not hold true in China, where family income had a negative effect on immunosuppressive non-adherence. Higher family income could potentially support transplant recipients in covering the costs of their immunosuppressants, monitoring immunosuppressant concentrations, and improving their quality of life [19]. Non-adherent patients were also more likely to be employed, which is explained by the fact that those patients were generally under greater time constraints [14].

## Individual-related factors

Among factors related to the clinical characteristics of the patient, which influence adherence, some authors highlighted the diagnosis of a mental illness, alcohol and other drug use, smoking, and the quality of life [8,12,20,21,31,35]. An increasing number of studies examining factors influencing adherence have delved into the issue of patients' mental well-being. It did not only involve diagnosing mental illnesses, but also pertained to various psychological states or traits, such as guilt, anxiety, and self-confidence. For instance, feelings of guilt in patients after heart transplantation were negatively associated with implication, persistence, and overall treatment adherence. Guilt was reported among cadaveric organ recipients who felt guilty about wishing for the potential donor's death. However, a study on living organ donation reported that guilt had no impact on treatment adherence [10]. Symptoms of anxiety among patients after transplantation were positively related to non-adherence [22,33]. In contrast, patients with higher acceptance of the illness exhibited better adherence behaviors [20]. Additionally, self-efficacy consistently emerged as a predictor of medication adherence in adult transplant populations, making it a likely target for interventional studies designed to improve medication adherence [23]. Patient attitudes were also shown to have an impact on adherence to immunosuppressive medications. Those with a confident and accurate attitude had a significantly lower variability of immunosuppressive medication levels in their blood [24].

Treatment experience during the period of organ failure may also influence subsequent adherence. In pediatric populations, hospitalization in an intensive care unit and the use of life support at the time of being listed for an organ transplant were both identified as important predictors of future adherence. Severe medical complications or hospitalization may motivate a patient or family to remain adherent to a medical plan [30]. This is especially pertinent for patients with no alternative treatment besides organ transplantation in case of a rejection.

## Therapy-related factors

Among the factors influencing adherence, both those related to treatment and others, several negative aspects were identified. These included the simultaneous use of multiple drugs or taking immunosuppressive tablets too many times per day [4,8,35], the lack of knowledge about the benefits of immunosuppressive medications or confusion regarding medication intake [8] or the dialysis period.

Simplifying dosing regimens has shown promise in improving adherence. For instance, reducing the dosing frequency from twice daily to once daily was found to enhance patient adherence [32]. Furthermore, decreasing the number of daily doses seemed to have a beneficial impact on patient adherence, addressing both missed doses and the timing of intake [34].

Notably, the side effects of immunosuppressive treatment may also have a negative impact on adherence. Kidney transplant recipients who reported higher levels of distress related to the side effects of immunosuppressive medications were more likely to be non-adherent. Recipients may attempt to reduce the symptom burden by adjusting their use of immunosuppressants [25].

A correlation was observed between good adherence and the dialysis period. It could be explained by the fear of returning to dialysis, which appeared to promote good adherence [26].

The time after transplantation was a distinct factor that influenced adherence [13,27,32], affecting not only medication adherence but also adherence to physical activity, blood pressure monitoring, non-smoking, maintaining a healthy diet, and other aspects. A possible reason for patients becoming less attentive to the medication regimen as time passed was that they felt better over time and no longer considered themselves as being ill [10].

### Healthcare system-related factors

Among factors categorized as healthcare system-related, the lack of health insurance covering the costs of immunosuppressive medications was the most commonly emphasized issue in the analyzed literature [36]. Furthermore, patient satisfaction with the frequency of scheduled visits emerged as a protective factor against non-adherence. While information about the facility's structure might not directly indicate clinical practices, one could speculate that in larger centers, the increased availability of human, equipment, and physical resources might facilitate more effective healthcare, improved patient self-management, and consequently, better adherence [28].

Monthly out-of-pocket expenses for immunosuppressants were identified as a risk factor for non-adherence and difficulty in paying medical bills was found to become an increasing issue in various countries [31].

### Cultural factors and ethnicity

According to available literature, cultural factors or ethnicity were identified to influence adherence to immunosuppressive medications. Research revealed that in Singapore, the non-adherence rate was 19.7%, which was lower than in Western societies. Several factors contributed to this situation, including lifelong government subsidies for immunosuppressive medications, the accessibility of transplant services, and cultural norms. In Singapore, patients were found to be more likely to adhere to medical instructions, deferring to the decisions of authority figures, such as doctors [3]. Another study demonstrated that the Black race was identified as a factor that decreased adherence [29]. Adherent patients exhibited higher internal religiosity compared to non-adherents [9], and patients with a religion other than Catholic or Protestant were more non-adherent, including those who declared no religious denomination [11].

### Methods to assess the adherence

Questionnaires constituted the most common method used in studies assessing adherence to immunosuppressive medication. One of the most popular self-reported questionnaires is the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS). The latest version is a 6-item instrument assessing the implementation (4 items), discontinuation (1 item), and initiation of related comedications [2]. The Immunosuppressant Therapy Adherence Scale (ITAS) is a four-item scale that may range from a low of 0, indicating very poor adherence, to the maximum score of 12, indicating perfect adherence [37]. Other scales used to assess adherence include the Morisky Medication Adherence Scale (MMAS) [38], Medication Adherence Report Scale (MARS-5) [39]. Microelectronic event monitoring is another method used in assessment of adherence. It is widely regarded as a highly reliable and sensitive method for measuring drug therapy adherence. It involves a microprocessor embedded in the medication bottle cap, recording each time the cap is opened and closed. These records allow for the tracking of missed doses and deviations from prescribed medication schedules [29].

## DISCUSSION

This review highlights the complexity of adherence to immunosuppressive therapy among organ transplant recipients. Despite the well-recognized necessity of maintaining strict adherence to avoid graft rejection and improve long-term survival, non-adherence remains a frequent and multifaceted problem. Reported prevalence varied widely, with rates ranging from 6% to 70% in adults and approximately 30% in pediatric populations, depending on the methodology applied. Such discrepancies emphasize the challenges of reliably measuring adherence, as different tools-ranging from self-reported questionnaires to blood drug levels and electronic monitoring-capture different aspects of patient behavior.

The study findings confirm that both intentional and unintentional non-adherence play an important role. Forgetfulness, disruption of routines, or medication unavailability were the most common unintentional causes, whereas intentional non-adherence was frequently associated with dose reduction or delaying refills, suggesting that the decision-making process is influenced by patients' attitudes and perceptions. This distinction highlights the need for tailored strategies: while unintentional lapses may be addressed by reminders or simplified regimens, intentional behaviors require more complex educational and motivational interventions.

Factors influencing adherence proved to be multidimensional, encompassing sociodemographic, individual, therapy-related, healthcare system and cultural domains. Younger age consistently emerged as a predictor of poorer adherence, with adolescence identified as a particularly vulnerable stage. In contrast, social support and stable family environment demonstrated a protective role, underscoring the importance of relational and structural contexts. Interestingly, higher education and higher income—typically expected to promote better health outcomes-were paradoxically linked with lower adherence in some populations, possibly reflecting greater autonomy in health-related decision-making or a perception of reduced vulnerability. These findings suggest that sociodemographic factors cannot be interpreted in isolation but should be considered within the broader cultural and healthcare system contexts.

Individual factors, particularly mental health and psychological traits, also had a marked influence. Anxiety, guilt and reduced self-efficacy were associated with poorer adherence, whereas acceptance of illness and higher self-confidence promoted more consistent medication-taking. These results align with broader evidence linking psychological resilience to chronic disease self-management

and highlight the need to integrate mental health support into post-transplant care.

Therapy-related aspects, including treatment complexity and side effects, emerged as critical barriers. Evidence suggests that simplified dosing regimens, such as once-daily formulations, improve adherence by reducing both missed doses and timing errors. Conversely, treatment burden, symptom distress, and adverse effects often motivated patients to intentionally alter their regimen, even at the cost of increased medical risk.

Healthcare system–related and cultural factors further shaped adherence. Lack of health insurance and high out-of-pocket costs were significant barriers in some contexts, whereas universal subsidies, accessible services, and strong cultural norms of medical deference, as observed in Singapore, facilitated adherence. Ethnicity and religiosity were also found to play a role, although evidence remains inconsistent and context-dependent.

Overall, this review demonstrates that adherence is a dynamic and contextually influenced process rather than a static patient trait. Effective interventions must therefore be multifaceted, combining simplified pharmacological regimens, educational initiatives, psychosocial support, and structural solutions within healthcare systems. Furthermore, the observed gaps, in particular the limited evidence on exclusively social determinants and their independent contribution to adherence-point to the need for further research employing standardized tools and robust methodologies. Such efforts could provide more precise insights and support the development of targeted, evidence-based strategies to optimize adherence and improve long-term transplant outcomes.

## CONCLUSIONS

### Implication to practice

This review demonstrates that adherence to immunosuppressive therapy is a dynamic and multifactorial process influenced by sociodemographic, psychological, therapy-related, healthcare system and cultural factors. Non-adherence remains a major challenge, shaped by both intentional and unintentional behaviors. In line with evidence-based recommendations of the American Society of Transplantation (AST) Adherence Task Force, effective strategies should include standardized adherence screening, longitudinal monitoring, and multicomponent interventions combining simplified regimens, tailored education, psychosocial and family support, and system-level solutions to reduce barriers [40]. Particular attention should be directed toward adolescents and other high-risk groups, who require targeted, structured interventions. Integrating educational programs, psychosocial support, and evidence-based adherence monitoring into routine post-transplant care may improve adherence and ultimately enhance long-term transplant outcomes.

### Strengths and weaknesses

This review has several notable strengths. Firstly, it employed a rigorous and transparent methodology, with predefined inclusion and exclusion criteria and independent assessment of articles by two reviewers, followed by consensus meetings with a third reviewer in case of disagreements. This procedure reduced the risk of selection bias and ensured the reliability of the review process. Secondly, the review covered an extensive time frame (1995–2023) and applied a structured search strategy using validated MeSH terms, thereby increasing the comprehensiveness of the retrieved literature. Thirdly, the narrative review approach allowed for the integration of findings from studies applying diverse methodologies and theoretical frameworks, enabling a broader and more nuanced interpretation of factors influencing adherence.

Nevertheless, this narrative review presents several limitations that should be acknowledged. Firstly, due to its non-systematic nature, the selection of studies may be subject to bias, as the inclusion criteria were guided by clinical relevance and expert judgment rather than a standardized systematic protocol. Furthermore, the absence of a meta-analysis limits the ability to quantitatively synthesize results or assess the statistical significance of identified factors. Many of the reviewed studies also differed in design, which, however, was the main rationale for choosing a narrative review methodology. In addition, only one database (PubMed) was searched, which may have resulted in the omission of relevant studies indexed elsewhere. Finally, the inclusion was restricted to articles published in English and Polish, introducing a potential language bias.

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