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Monitoring Drug Adherence

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Abstract

Topic—Medication nonadherence is prevalent in transplant recipients and is a major reason for graft loss. The present review discusses the measurement of adherence in transplant recipients and strategies to improve adherence.

Sources reviewed—since adherence research is not confined to transplant recipients, our literature review included studies relevant to transplant recipients as well as adherence to medical recommendations more generally. We reviewed manuscripts in the English language indexed in PubMed Central, as well as ancillary sources of information such as textbook chapters that are not indexed.

Conclusion—There is no consensus in the literature about an optimal way to monitor adherence, nor is there agreement about a preferred management strategy. Until definitive studies demonstrate the effectiveness of intervention strategies, knowledge of the monitoring as well as intervention methods that are described in this review is expected to give practitioners the initial tools to deal with nonadherence as an important aspect of patient care.

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Nonadherence to medical recommendations is a leading cause of morbidity and mortality in a wide array of disease processes in all age groups.^{1–8} Adherence is especially important in patients with chronic or complex medical conditions such as transplantation, who need to

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adhere to lifelong medication and dietary regimens. For these individuals, adherence is of the utmost importance given its association with health outcomes.

Extensive data strongly suggests that nonadherence is a significant cause of morbidity and mortality in post-transplant patients.^{2,3,9–13} More specifically, nonadherence to immunosuppressant therapy is considered to be the leading cause of preventable graft failure¹⁴, contributing to 20 % of late acute rejection episodes and 16 % of graft losses within the overall transplant population¹⁵. Yet, in clinical practice, there lacks a systematic approach to identifying and treating nonadherence. In this review, we focus on the clinical importance of medication nonadherence in transplant recipients. We discuss the role of drug monitoring, among other methods of measuring nonadherence, and review various techniques to improving nonadherence in the clinical setting.

Definition of Nonadherence

The term nonadherence is used to describe general behaviors that deviate from a prescribed health regimen¹⁶. More specifically, nonadherence encompasses numerous behaviors that jeopardize health outcomes including: 1) improper medication adherence (e.g. forgetting to or intentionally not taking medications as prescribed), 2) failure to obtain recommended laboratory/radiographic testing, 3) failure to attend clinic visits, 4) and failure to adhere to certain lifestyle behaviors that promote good health (e.g. dietary restrictions and exercise). In this review, we focus on nonadherence to immunosuppressant medications given its significant impact on graft outcomes.

Strict adherence to prescribed medications should not be the goal in clinical practice, given that many patients engage in some form of nonadherent behavior¹⁷, and not all nonadherent behaviors lead to adverse health outcomes. Presumably, most clinicians would agree that minor infractions do not constitute “nonadherent behavior”. From our perspective, there is little evidence to suggest that minor deviations from a prescribed protocol actually compromise medical outcomes. For example, a transplant patient who is prescribed tacrolimus every 12 hours may occasionally take the medication on a slightly different schedule (e.g. 8 am and 10 pm instead of 7 am and 7 pm). Most clinicians would not consider this slight variation in medication administration as a reflection of nonadherence, at least not in a clinically significant way. Moreover, most clinicians would agree that this patient likely should not be treated for nonadherence. The key is motivating patients to take their medications well enough so that adverse events are avoided¹⁸.

The question remains, what degree of nonadherent behavior leads to clinically significant outcomes? To determine an adherence threshold level (e.g., “it is okay for this patient to forget to take the medication once a week but not twice a week”), one must determine at what point medical adverse events are likely to arise.¹⁹ In order to determine which degrees of nonadherence are clinically important, it is imperative to establish how to recognize and measure nonadherence accurately.

Measurement of Adherence

There is no gold standard for the measurement of adherence, and each proposed method has its shortcomings.²⁰ A comprehensive review of assessment methods is beyond the scope of this manuscript; however, a brief summary and analysis is warranted. Methods of measuring nonadherence fall into two different groups: 1) direct measures of adherence including observed therapy and measurement of drug/metabolite levels, and 2) indirect measures including patient surveys, rate of prescription refills, electronic medication monitoring, and medical record documentation. Each method has its limitations, and many techniques remain to be validated²¹.

An “ideal” measure of nonadherence should be objective, direct, pose little burden to the patient, and provide actionable information about patient adherence to the clinical team (and perhaps even to the patient herself / himself and other caretakers). Unfortunately, in the clinical setting, most measurements of nonadherence include subjective methods such as self-report via questionnaires or clinician-documented observations in an electronic medical record (EMR)¹⁷.

Other indirect measures of nonadherence including electronic pill bottles, medication refill rates, pill monitoring programs, may sometime be accurate (although patients using electronic cap systems can easily discard a pill from a bottle without actually ingesting it), but pose risks for selection bias and excess cost. It is important to realize that nonadherent patients— who are by definition not following medical recommendations— are also not likely to follow recommendations to monitor their medication intake. Therefore, patients likely to use elaborate electronic monitoring devices including even direct measurement methods such as ingestible sensors²² are also likely to be more adherent than the general population: precisely those patients who are less likely to need help with adherence. Thus, even if these methods have the potential to provide more precise information about a patient theoretically, they may be less desirable if they do not capture the population most at risk. Therefore, although they are sometimes described as the new frontier in adherence monitoring²³, electronic monitors or specialized chips, and other innovations, while intriguing, are not likely to lead to significant improvements in outcomes unless their use is entirely streamlined with clinical procedures and patient burden is minimized. We agree with others²⁴ that use of these devices or innovations should be subjected to systematic scrutiny before they are actually implemented in practice. In contrast, the direct observation of the ingestion of a pill would provide solid proof of adherence. But this procedure is highly impractical. Thus, while direct measures are clearly more accurate, they might be more burdensome to the patient and costly to the health care system.

The last among direct measures of adherence includes medication levels and drug level variability. Variation in immunosuppressant levels has been shown to be a robust measure of nonadherence^{9,25}. More specifically, the standard deviation of immunosuppressant levels has not only been shown to be a good measure of nonadherence in liver transplantation, but also a good predictor of graft failure²⁶. Hence, drug level variability may be a useful measure of nonadherence that could be used with ease in the clinical setting. It may be

combined with other less specific measures of nonadherence including clinician assessment or self-reporting in a “tiered” approach.

A meta-analysis²⁷ suggested that subjective methods (e.g., questionnaires) may be at least as good as, or even better than, objective methods to assess adherence, based on the finding that subjective methods, when grouped together, yield a seemingly higher rate of nonadherence than objective ones. The problem with this assertion is that a higher rate is not necessarily an accurate rate, and that grouping together studies that use different thresholds of adherence or methodologies is not ideal, especially when meta-analytic techniques are used. In a cross-sectional study of kidney transplant recipients, electronic monitoring, immunosuppressant drug assay, patient self-report, and physician collateral report were compared in regards to diagnostic accuracy of medication nonadherence²⁸. Individual measures of non-adherence were found to have poor sensitivity, whereas a composite adherence score compiled of nonadherence information from patient self-report, medical team collateral report, and drug assay had the highest sensitivity. Combined assessments may have a role, but are very hard to implement in clinical practice¹⁸. Because of the significant burden involved in implementing a combined assessment strategy as compared with a “tiered” approach, in order to be accepted, we believe that those strategies must be evaluated in well-powered, prospective studies that define the way the methods would be combined prior to the beginning of the study and not post-hoc¹⁸.

In conclusion, because of the known problems with self-reports^{17,29–33}, in our view the acceptable standard for assessment of adherence should be an objective measure. Self-reports may still be used to supplement objective assessments, perhaps as a ‘first tier’ assessment in the context of a robust adherence monitoring program.

Risk Factors for Nonadherence

Risk factors that have been reported to be associated with nonadherence to medications may be grouped into those that are associated with the disease itself, the treatment, the patient, the social milieu, and the healthcare team. These domains overlap, and risk factors are shared between groups.

Specific characteristics of chronic medical illnesses, for example, cognitive decline (e.g. subacute hepatic encephalopathy as a complication of chronic liver disease) may predispose a patient to become nonadherent.^{34–36} Furthermore, the characteristics of the disease process³⁷, such as chronicity, may influence the risk of nonadherence. The characteristics of the treatment regimen are also important. Treatments that are time-consuming, require a high level of organization (e.g., multidrug regimens), and require a high level of motivation all carry an increased risk of nonadherence.^{38–40} Treatments that have a severe spectrum of side effects are sometimes,^{41–43} but not always,^{44–45} reported to carry a higher risk of nonadherence. The nature of the recommendation is also important; lifestyle changes (i.e., dietary) are thought to be hard to achieve, perhaps because lifestyle changes require a more complex behavior.⁴⁶

The patient’s conception of illness and psychological reaction to experiencing a chronic illness affects adherence⁴⁷. Distress that is specifically related to the illness^{48–49}, as well as

more specific psychopathology, predict nonadherence. For example, the occurrence of depressive disorders^{50–52} and post-traumatic stress disorder,^{49,53–54} was consistently found to be related to nonadherence. Reported feeling of “lack of control,”^{55–57} and the use of avoidant coping^{53,57} have all been implicated in nonadherence.

A lack of empathy on the part of the clinician and a lack of trust between the patient and the clinician have been implicated in patient nonadherence.^{58–59} Lack of appropriate information about medications also poses a plausible reason for nonadherence, but lack of information alone may not be a sufficient cause for nonadherence in many cases.⁶⁰ Finally, the characteristics of the clinic can be important to the development of adherent behavior in patients.⁶¹

Treatment of Nonadherence

While strategies to improve adherence have been promoted as important and recommended by several professional societies⁶², the sobering truth is that no single intervention has ever conclusively been shown to improve post-transplant outcomes, and in fact, adherence-improving techniques rarely show improvement in any clinical population. For example, a recent analysis⁶³ concluded that “Among 57 studies measuring clinical outcomes, only 8 reported a significant improvement in clinical outcome.” The reasons for this surprising and disheartening finding are complex. We point out a few of the challenges facing interventional research in adherence studies and that make them less likely to succeed in improving medical outcomes.

1. Selection bias. As mentioned previously, nonadherent patients are less likely to follow medical recommendations and thus are also less likely to participate in research, or to follow study procedures if they do consent. Therefore, most adherence studies are seriously biased and do not accurately represent the general clinical population that they study⁶⁴. Because adherent patients are precisely those who do not need the intervention, it is very difficult to show any positive medical outcomes in controlled studies^{65–66}.
2. Selection of outcome variables. Another feature of a selection bias is the fact that some improvement in adherence per se is actually easier in patients who are adherent at baseline, and harder in patients whose adherence is severely compromised. For example, improving patient adherence from 75% to 85% over a study period is quite possible, because patients who are already showing a high degree of adherence are more likely to follow study procedures and improve their adherence even further. However, the medical outcomes of those patients are not likely to improve much, since the marginal improvement of adherence from 75% to 85% is not sufficient to affect outcomes. In contrast, an adherence improvement from 40% to 70% might make a substantial difference in outcome, but is much harder to achieve. Thus, studies that choose a primary outcome of “adherence improvement” may show a significant improvement in adherence but fail to show improvement in actual clinical outcomes⁶⁵. Because of this issue, in our view, the standard for determination of efficacy of adherence interventions should be

improvement of pre-defined, robust important clinical outcomes rather than improvement in adherence.

3. Inability to focus on the correct subset of patients. Adherence behavior is best viewed as a continuum – some patients adhere more than others; only behaviors that reach a certain threshold are problematic. Implementing a robust adherence assessment method is hard for reasons mentioned above. Therefore, almost all adherence studies (and clinical interventions that purport to systematically address adherence in clinics) address entire clinics or at-risk patient groups^{67–69}, but not only patients who are a-priori identified as nonadherent. For example, in a recent report of the use of remote communication technology to assess adherence, such as electronic texting devices or hand-held mobile devices, an effort to pre-identify the nonadherent patients was not even mentioned²³. This leads to several serious flaws. First, since nonadherence is not ascertained as an inclusion criterion, it cannot be specifically targeted. For example, an intervention cannot attempt to mitigate avoidance behaviors, rendering the intervention effort less effective. Second, the intervention is delivered to a wide range of patients, some of whom may need it and some who may not (as their adherence status is not known at the outset), making the approach far less cost-effective. Third, the effect size of the intervention might appear to be small, even if it could have been effective with the correct population. Fourth, intervening with patients who are already adherent (e.g., sending frequent text message reminders) could, in some cases, lead to patient frustration and reduced adherence.
4. Adherence behavior, as mentioned above, may have many “root causes” and predisposing risk factors. An intervention addressing one specific construct is likely to be non-responsive to the needs of a significant proportion of patients who may have other concerns. On the other hand, a non-specific approach is difficult to study and even more difficult to implement responsibly.

In our view, the ideal adherence intervention strategy would involve several facets: continuous monitoring of adherence through a direct measure such as medication variability; identification of patients who are nonadherent using a monitoring threshold; evaluation of risk factors, addressing any identified or possible risks while trying to eliminate avoidance behaviors as those commonly interfere with treatment⁷⁰; and continuous monitoring and re-intervention as needed²¹. Nonadherence is best viewed as a waxing and waning chronic risk, not as a disorder that can be “cured” in a one-time effort²¹. The following are capsule reviews of strategies that may be useful in improving adherence in specific patient subgroups.

Prevention of Nonadherence

The hallmarks of prevention involve the provision of general and specific education about medication taking that is delivered in a culturally sensitive manner, repeated frequently, and targeted to the patient’s abilities. Patient education has been identified as the most common preventative adherence-enhancing intervention that is used clinically in transplant settings⁶⁷.

Patient Education

Targeted education, as distinct from general education which is mentioned above, is an interactive process in which the clinician tries to identify the cognitive and procedural needs of the patient and address them. It involves an assessment of the patient's understanding of the prescribed regimen, its administration, and the reasons for it; the correction of any misinformed notions that are discovered; and an open discussion about the ways in which the medication is being taken, how it can be better integrated into a patients' lifestyle, and what concessions or resources are needed to make medication-taking possible. Inquiring about the patients' own perceptions as a part of the educational process⁷¹ is a component of shared decision-making strategies. Such an integrative educational approach may benefit from an active participation of a pharmacist^{65,72}.

Behavioral Modification Strategies

Behavior modification strategies can be used to implement a reward system for adherence (i.e., a child is rewarded with a sticker every day he is able to take his medications without being reminded). Behavioral methods could also include a change in the frequency in which the patient is seen in the clinic to improve the physician's control on adherence, or casemanagement including "contracting for adherence"⁶⁵. Behavioral methods usually necessitate the involvement of another caretaker, a clinician, or a therapist. Behavior modification strategies have been reported as helpful in improving adherence.^{73,74} However, the efficacy of these methods in the improvement of medical outcomes in transplant recipients has not been rigorously evaluated, and some approaches were not shown to improve medical outcomes⁶⁵. In addition, some behavioral methods require a specifically trained individual who may be required to serve as a "coach" to patients⁷⁵. This individual may not be readily available in many clinics. Finally, because strict adherence to the behavioral intervention is required for success, it may at times be difficult to implement these methods in patients who are nonadherent to recommendations to begin with.

Cognitive-behavioral approaches

Cognitive-behavioral approaches, which add a "cognitive restructuring" component that addresses patients' beliefs and dysfunctional coping mechanisms to behavioral approaches is a standard component of many psychotherapies. Surprisingly, such approaches have not been adequately studied in transplant recipients, although pilot studies suggest that this modality might benefit a select group of patients^{49,76}.

Strategies Aimed at the Improvement or Elimination of Risk Factors

There are many known or suspected risk factors for nonadherence, as mentioned above: some of those may be highly modifiable. For example, the treatment of a specific psychiatric disorder such as a major depressive disorder or post-traumatic stress disorder^{77,78} may improve adherence. Improvement of social stressors and provision of safety, such as the elimination of domestic abuse and enhancing resilience amongst at-risk patients may be reasonably expected to improve adherence as well⁷⁹. The identification and management of risk factors related to the patient and his/her environment should therefore be attempted.

When applicable, the assessment of risk should extend at least to the primary caretakers as well.

Conclusions

Extensive data demonstrate that complete adherence is, in fact, hard to attain in clinical settings⁸⁰. Therefore, adherence should not be assumed. Rather, the attainment of adherence to recommendations must be included as a treatment goal^{80,81}. As reviewed above, nonadherence to medical recommendations is a significant, and mostly modifiable, risk factor for increased morbidity and poor outcomes in transplant recipients. There are no “gold standard” methods for assessment of nonadherence, but several objective and subjective methods do exist. The management of nonadherence might include preventive, nonspecific efforts that start with proper patient education, shared decision-making strategies, and rapid identification of suspected cases. Specialized treatment strategies that focus on education, behavior management, and addressing specific risk factors can then be mobilized. Adherence research must move beyond the demonstration of improvement of the behavior itself (adherence), which may be relatively easy to achieve, and into researching strategies that improve robust, pre-defined, medical outcomes. Until such time as definitive studies demonstrate the effectiveness of an intervention, knowledge of the methods that are described in this review is expected to give practitioners the initial tools to deal with nonadherence as an important aspect of patient care.

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