Transplant International

INVITED COMMENTARY

Medication trade-offs—Not all noncompliance is what it seems

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Transplant International 2018; 31: 861–863

Received: 30 April 2018; Accepted: 1 May 2018

Admit it. More than once, you have scanned a transplant journal, searching for a novel topic, something different from the many ubiquitous registry reviews. You hope you can find something topical, relevant for your patients and timely to current events. You probably did not even realize this issue of Transplant International would be the one containing that very topical, relevant, and timely manuscript. The article by Serper *et al.*[1] "The Prevalence, Risk Factors, and Outcomes of Medications Tradeoffs in Kidney and Liver Transplant Recipients" examines a subject that seems familiar at first glance, but is actually one that has not been studied or reported in great detail. The authors work is so timely, because these issues are presently in flux and evolving—even as this editorial is being written. U.S. lawmakers are currently debating the survival of the Affordable Care Act, the fate of patient insurance subsidies, and the overall accessibility of health insurance and care in the U.S., and by the time this article is even published, events may further amplify the significance of the data these authors present regarding the impact of medication trade-offs.

Trade-offs are defined by the authors as "an inability to afford medications, spacing out medication frequency, or choosing between buying medications and food". Given that prescription medication costs are the fastest growing segment of healthcare expenditures in the U.S. [2], and also, given that transplant recipients are dependent on expensive, lifelong, immunosuppression [3], it is not surprising that transplant recipients would be some of the most impacted by the financial considerations resulting in trade-offs. Serper *et al.* is the first study to examine the issue of medication trade-offs in transplant recipients, in how often recipients make choices in taking their meds, and it is an impressive undertaking, prospectively analyzing 201 transplant recipients from two geographically distinct U.S. transplant centers. The authors were comprehensive in their social assessments, using five separate validated study questionnaires to broadly characterize the study population and identify potential trade-offs: (i) Medication Tradeoffs (USDA Insecurity Questionnaire); (ii) Health Literacy (Newest Vital Sign Questionnaire; (iii) Global Cognitive Function (Mini–Mental State Examination; (iv) Social Support (Lubben Social Network Scale; and (v) Medication Adherence (Patient Medication Adherence Questionnaire).

The study found that 17% of liver and kidney recipients reported a medication trade-off, the most common being an inability to afford a prescription in the past

doi:10.1111/tri.13279

12 months, as well as making a choice between prescriptions and food, both of which impacted 11% of recipients. The most affected recipients were those between the ages of 31–45 followed by those in the 46–54 age group. While the univariate analysis showed trade-offs were reported more often in patients with incomes less than $20 000 (44% vs. 15%) and in African Americans compared to whites (34% vs. 11%), a multivariate analysis found the independent predictors for medication trade-offs were (i) patients on Medicare; (ii) those having greater than 3 comorbid conditions; (iii) those with limited health literacy (defined as the ability to comprehend and use health information to make health decisions). There was no difference in the presence of trade-offs between liver and kidney recipients; however, the timing of these trade-offs varied between the two organs. Liver recipients are more likely (59%) to face trade-offs in the first 12 months, likely a function of the period where the number of medications was highest. Conversely, kidney recipients are more likely (53%) to face trade-offs at 3 years post-transplant, probably related to the fact Medicare covers 80% of immunosuppression costs for the first 3 years, which ceases after 3 years, shifting the financial strains for many to that time.

In the age of the SRTR Database, where graft and patient survival are tracked, insurance companies use that data to rate the transplant programs, meaning the status of a U.S. transplant program can hinge on a fractional percentage point change in the SRTR data [4]. With medication trade-offs impacting at least 17% of transplant recipients, while being associated with increased complications, it would behoove transplant centers to evaluate their recipients for these trade-offs to enable potential interventions. Additionally, the presence of a medication trade-off is associated with a 64% increased risk of a hospital admission, making the identification these at risk for trade-offs a potential cost-effective measure. The risk of hospital admission increased further with increasing number of trade-offs, with a hazard ratio of 1.63 (CI 1.03–2.60) for one trade-off and 1.84 (CI 1.12–3.02) for two or more trade-offs. From a Medicare point of view, the saving from avoiding the increased hospital admissions might offset the cost of the government extending immunosuppressive coverage.

If there is a weakness in the manuscript, I believe the authors do not go far enough in describing how trade-offs differ from what transplant centers consider noncompliance, and why those differences are relevant to why trade-offs may go unrecognized. Noncompliance is the Achilles heel of transplantation, because it leads to increased complications, allograft failure, and mortality, even in patients with a successful perioperative and postoperative course [5]. Transplant centers work to identify noncompliant candidates during the recipient selection process, to maximize the successful outcomes of limited organ supply [6] utilizing social work and psychiatric evaluations to identify barriers to success and those prone to noncompliance. Frequently, a patient's attendance at pretransplant appointments and diagnostic studies can be a valuable proxy for post-transplant compliance, and in the case of kidney transplant, dialysis attendance records are excellent markers to identify a diligent and compliant patient. The goal is to identify patients who are careless or disinterested in their health care.

While transplants centers are geared to identify noncompliance, their screening techniques might miss identifying medication trade-offs, despite similar origins. Trade-offs are different than noncompliance as trade-offs occur when a person is forced to make a choice due to circumstances, between medications they cannot afford or between medication and necessary items such as food. Where noncompliance is often rooted in a laissez-faire and disinterested approach to self-care, trade-offs in contrast are a conscious and often precise, careful response to circumstances. Deciding to spread out medications to make them last longer because of lacking financial resources, is an entirely different action than forgetting to take one's medication. The study demonstrates this fact, as patients who reported trade-offs had lowered self-reported adherence for medications for chronic diseases, but not for their immunosuppression, meaning they were making a precise decision to prioritize immunosuppression. Ironically, many of the chronic diseases that occur post-transplant requiring long-term medications (diabetes, hypertension, and renal insufficiency,) are often caused or worsened by immunosuppression [6,7], meaning the nature of transplantation itself indirectly potentiates the need for medication trade-offs [8].

Unlike noncompliance, medication trade-offs are dynamic, as trade-offs can develop when social, financial, and medical parameters evolve in the post-transplant period. Changes in insurance coverage, income, or social support may elucidate medication trade-offs where none existed prior. It is why the current attempts in the U.S. to eliminate healthcare subsidies in the Affordable Care Act are so relevant to the results from this study, and why it may have significant future implications for transplant centers and their patients.

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Recognizing the importance of medication trade-offs requires a new paradigm for evaluating recipients in long-term post-transplant follow-up. It will involve clinicians wading into socio-economic topics of education, race, literacy, and poverty—topics some surgeons are wont to avoid. The findings from the univariate and multivariate analysis of this study help us to identify patients at higher risk for trade-offs—but more is needed. While health literacy and socio-demographics can be identified in the pretransplant period, any potential intervention to limit the impact of trade-offs will require routine, brief social assessments in the long-term post-transplant period to examine finances, social support, and ability to afford medication.

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