EDITORIALS

The Importance of Social Ties in Sustaining Medication Adherence in Resource-Limited Settings

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Ten years ago the late John Eisenberg, along with Elaine Powers, elaborated a conceptual framework to explain unachieved potential for high-quality care delivery in the US, analogous to the voltage drops that occur as an electrical current flows through a series of resistors.[1] Using an adapted version of their framework, one can appreciate that a mix of public health and health care strategies will be needed to address the growing burden of cardiovascular disease in resource-limited settings. Many countries' efforts to reduce cardiovascular risk at the population level are hampered by unaffordable (or unavailable) health insurance schemes; fragmented, acute care-oriented health care systems; and weak primary care infrastructures.[2,3] Even if these sizable voltage drops are addressed, potential quality will be further dissipated through another series of resistors: patients must seek evaluation for treatment[4]; health care workers must be consistently available[5] to provide patients with accurate diagnostic assessment,[6] either through clinical examination or blood testing; appropriate treatment must be prescribed,[7] whether pharmacologic or non-pharmacologic (e.g., lifestyle change); and patients must adhere to prescribed treatment.[8]

Maximizing treatment adherence is the final step needed to translate potential access to health care into improved outcomes. Adherence consists of two related constructs: (1) persistence, or the duration of time from initiation to discontinuation of therapy; and (2) dose-taking execution, or the proportion of doses taken as prescribed prior to discontinuation.[9,10] In high-income countries, suboptimal dose-taking behavior by persons with different types of chronic illnesses is well-documented.[11] In resource-limited settings, however, less is known about dose-taking execution by persons with chronic illnesses other than HIV. In this issue of the *Journal*, Bowry et al.[12] provide the first systematic review and meta-analysis of dose-taking behavior in the setting of cardiovascular medication use in the emerging and developing economies of Africa, Asia, and Central and South America. Across 76 studies, 57.5% of participants were classified as adherent. To place this finding in context, a previously published meta-analysis of 129 cardiovascular medication adherence studies conducted in high-income countries estimated that 76.6% of participants were classified as adherent.[11]

Dose-taking execution is typically measured on a continuous scale as the average percentage of pills prescribed for a specified time window actually ingested. However, the meta-analytic findings of Bowry et al.[12] were based on the proportion of *persons* classified as adherent (e.g., "regular medication use," "≥85% of pills taken"). Data on the average proportion of *doses taken* were presumably unavailable. Their experience was consistent with that of DiMatteo,[11] who reported that data on average doses taken were only available for 3% of the 569 studies included in her meta-analysis.

The practice of dichotomizing data on dose-taking execution to classify persons as adherent or non-adherent has a long history in clinical research and has been characterized pejoratively as being "patently devoid of pharmacodynamic content."[13(p.587)] The choice of cutoff may be arbitrary (>66%),[14] less arbitrarily based on natural breaks in the data (≥90%),[15] or empirically derived from the clinical response to treatment (≥95%).[16] When continuous variables are dichotomized in this fashion and used in primary analyses—rather than, for example, in secondary analyses to enhance exposition of the primary findings—valuable distributional information is lost. Subsequent analyses using the dichotomized variables as predictors[17–19] (i.e., to assess the effect of dose-taking execution on clinical outcomes) or as outcomes[20,21] (i.e., to identify facilitators of or barriers to adherence) tend to suffer from loss of efficiency and various biases.

Bowry et al.[12] did not report on persistence to treatment, as this was beyond the scope of their study. Persistence deserves additional scrutiny by researchers studying chronic illness care in emerging and developing economies for several reasons. First, dose-taking execution and persistence may not necessarily coincide. One can sputter along indefinitely with a set of medications yet execute the prescribed regimen poorly, taking doses with variable punctuality or omitting a large proportion of doses entirely. Conversely, one can take all doses in a timely fashion without persisting with the regimen for the entire prescribed duration of treatment. Second, studies of adherence to pharmacological treatment for chronic illnesses have documented declining dose-taking execution[22] and persistence[23] over time, and this bodes poorly for the long-term success of treatment scale-up for persons with uncurable but manageable chronic illnesses who face a lifetime of pill-taking. Third, depending on the pharmacokinetic properties of the specific medication under consideration, a high degree of punctuality in average dose-taking execution can still result in poor outcomes if the rare episodes of

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non-persistence (described variously as drug holidays,[9] treatment interruptions,[24] or non-permissible gaps[10]) are sequentially concentrated in time.[24,25]

Comparing the findings of Bowry et al.[12] to those of DiMatteo[11] might lead one to conclude that dose-taking execution of cardiovascular medication regimens is worse among patients living in emerging and developing economies, and that the primary barriers they face are cognitive in nature. This is notably different from what has been reported in the HIV literature. Dose-taking execution of HIV antiretroviral therapy has been shown to be at least as good, or possibly better, among persons living with HIV/AIDS in sub-Saharan Africa compared to those living in the US and Canada.[26] And, while barriers like inadequate knowledge, side effects, and regimen complexity adversely affect adherence in any setting, studies of HIV antiretroviral therapy adherence suggest that structural and economic barriers may be more relevant factors in resource-limited settings.[27–29]

These puzzling discrepancies might be explained by the ways in which the social dynamics of treatment for these chronic illnesses differ in resource-limited settings. People living with HIV/AIDS in sub-Saharan Africa often initiate HIV antiretroviral therapy at advanced stages of illness characterized by severe debilitation.[30] By the time they have initiated treatment, they (and their caregivers) have long been removed from contributing to the income-generating and food-producing activities taking place within their network of social ties.[31] Treatment often leads to a rapid and profound return to productive functional status (described as the "Lazarus effect"[32,33]) and a renewed ability to contribute economically to their social networks.[34] Their social networks, in turn, are motivated to help them overcome structural and economic barriers to adherence so that their economic contributions can be sustained.[28] In the case of medications aimed at reducing cardiovascular risk in resource-limited settings, we hypothesize that treatment adherence, functional status, and social ties are not as tightly linked. The same structural and economic barriers exist,[2] but cardiovascular medications are primarily aimed at preventing future loss of function rather than restoring lost function. As such, it may be more difficult for patients taking cardiovascular medications to draw on their social ties for assistance in adhering to treatment.

The increasing burden of cardiovascular disease in sub-Saharan Africa[2,3] and in other emerging and developing economies[35] militates for the expanded use of interventions to improve chronic illness care in these settings.[36] Some strategies might be adapted from those already used in treatment scale-up for persons living with HIV/AIDS,[37] but more research to develop innovative interventions to optimize adherence to medications used to reduce cardiovascular risk are sorely needed. Bowry et al.[12] show that we have a long way to go.

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