



Unrecognized nonadherence masquerades as drug resistance

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Nonadherence to medical regimens, or the failure to take drugs on time in the dosages prescribed, is as harmful and costly as many illnesses. Nonadherence is common, contributing to worsening disease, increased healthcare costs, and death [1]. One-third of the prescriptions written each year is never picked up, and of the 2 billion prescriptions filled one half are taken incorrectly. The resultant cost in the United States is approximately US\$ 100 billion a year [1]. Nonadherence accounts for 125 000 deaths annually and leads to 10–25% of hospital and nursing home admissions. Adherence is generally defined as the extent to which patients take medications as prescribed by their healthcare providers. For ambulatory patients it is the link between medical process and treatment outcome [2]. As the former US Surgeon General C. Everett Koop famously observed, ‘Drugs don’t work in patients who don’t take them’. Patient nonadherence is a global issue of major public health concern with consequences for all of us – patients, caregivers, healthcare practitioners, researchers, employers, and taxpayers. One in three patients never fills the prescription. Others skip doses, take their pills at the wrong time or take too much or too little [3]. Some take medicines that have not been prescribed. Many who follow recommendations at the start eventually stop taking the medication altogether [4]. Sackett and Snow [5] advanced the estimate that only about 50% of patients with chronic diseases take their medicines at therapeutically effective doses. A *New York Times* health reporter proclaimed nonadherence as the world’s ‘other drug problem’, [6,7] but because nonadherence has not been regarded as a public health problem it has generated little systematic intervention [6]. The ability of physicians to recognize nonadherence is poor, and interventions to improve adherence have produced, at best, mixed results.

A major challenge in the treatment of asthma is its heterogeneity and the variability of response to standard treatments, most notably to inhaled corticosteroids (ICS) [8,9]. Of equal importance, nearly 70% of patients with severe asthma do not refill prescriptions for ICS, and many use inhalers

improperly [10]. Recently RAND Corporation reported the results of a retrospective observational study using 2 years of claims data for 41 234 commercially insured asthmatic patients on standard monotherapy. The median medication possession ratios were 39% for leukotriene inhibitors and 15% for ICS [11].

In the past year the *New England Journal of Medicine* has published two benchmark articles that account for some of the variability in the therapeutic responses by patients with asthma [12,13]. One of the studies identified a functional glucocorticoid-induced transcript 1 gene (GLCCI1) variant associated with substantially decreased response to ICS [13]. The other showed in a subgroup of patients with asthma poorly controlled with ICS that treatment with an antibody to interleukin 13 led to a significant improvement [12]. In both studies the patients’ poor response to ICS was a matter of utmost importance. We wish to call the readers’ attention to the role of adherence in clinical trials because the knowledge of adherence is essential to distinguish between therapeutic nonresponders and individuals who do not take their medicine. Variable adherence vies with pharmacokinetics as the leading source of variance in drug response in ambulatory settings. Nonadherence acts to diminish the apparent magnitude of the drug effect and thereby acts to decrease power. It confounds and undermines the results of clinical trials. By not addressing this issue, the authors of the two studies may have underestimated the significance of their data [12,13].

We must be aware that unrecognized nonadherence masquerades as drug resistance. The only way

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to tell apart those patients who do not respond to their medications from others who do not adhere to their clinical regimens is to monitor adherence. Collecting adherence information should become a part of routine care of patients who are failing therapy and an essential part of most clinical trials. We need accurate assessment of patient adherence in clinical trials and in practice. We also need novel statistical methods to account for the effect of adherence on the outcomes of clinical trials [4]. We propose that the clinical trials community incorporate adherence monitoring in the study design for large collaborative medication protocols and that journal editors request adherence data in considering manuscripts for publication.

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Conflicts of interest

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