EDITORIAL

Nonadherence, Clinical Inertia, or Therapeutic Inertia?

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In our editorial work with manuscripts, the terms "clinical inertia" and "therapeutic inertia" have been used recently by authors, primarily to attribute to physicians the apparent failure of patients to attain therapeutic blood pressure goals. We think it would be helpful to define and differentiate these terms. In this editorial, we explore the meaning of the terms clinical inertia and therapeutic inertia, relying on the previous work that has been performed. We also explore some factors contributing to clinical inertia and examine the reliability of clinical guidelines based on biomarkers as benchmarks to measure the apparent inertia of treatment.

A PubMed search on the term "therapeutic inertia" performed in August 2009 produced 21 citations. Therapeutic inertia first appeared in the MEDLINE-indexed literature in an article by Andrade et al. in July 2004.[1] Andrade et al. used the term "therapeutic inertia" twice, referring to an article written by Phillips et al. (2001) with the title "Clinical Inertia," which did not mention therapeutic inertia anywhere in the article.[2]

The article by Andrade et al., which apparently created the term "therapeutic inertia," perhaps inadvertently, is later referenced in an article by Okonofua et al. (2006) that defined therapeutic inertia as the "failure of providers to begin new medications or increase dosages of existing medications when an abnormal clinical parameter is recorded."[3] This definition is nearly identical to the definition of clinical inertia put forth 5 years earlier by Phillips et al.: "failure of health care providers to initiate or intensify therapy when indicated" and "recognition of the problem, but failure to act."[2] Okonofua et al. also reduced the simple 2-word phrase to an acronym (TI), perhaps in an attempt to lend more credibility to the concept (we eschew 2-word acronyms, but if TI is used at all, it should refer to therapeutic interchange).[3]

While there is additional history behind the use of the terms "clinical inertia" and "therapeutic inertia," much of the more recent usage is imprecise. We think that it is time to use these terms more carefully and more purposefully and to refer to models that have some basis in theory and evidence. We propose specifically to use the term "clinical inertia" to encompass a host of factors in at least 3 categories, as described by O'Conner et al. (2005): physician factors, patient factors, and office system factors.[4] The research regarding clinical inertia is more rigorous, and clinical inertia was defined first and is the preferred term.

Clinical inertia is an important theoretical construct that encompasses the underuse of therapy that is efficacious and effective in preventing serious endpoint clinical outcomes such as death, nonfatal myocardial infarction (MI), and stroke. Underuse of therapy is particularly important in common chronic diseases in which certain therapies have adequate, even overwhelming if not unequivocal, evidence of effectiveness.[5] Clinical inertia occurs, for example, when the patient fails to attain a biomarker goal (e.g., blood pressure less than 140/90 millimeters of mercury [mm Hg]) due at least in part to failure to intensify pharmacotherapy through upward dosing and/or addition of drugs to the therapeutic regimen. O'Connor et al. attributed clinical inertia 50% to physician factors, 30% to patient factors, and 20% to office-system factors.[4] We might consider the latter category even more broadly to include all health-system factors (Table 1). While we are uncertain about the relative weights for these 3 categories of factors that contribute to clinical inertia, we propose that this conceptual model, including relative weights, should become a focal point in research in nonadherence and failure to attain biomarker and other clinical goals.

While acknowledging access, cost, and patient nonadherence, Phillips et al. emphasized the role of clinicians when they wrote in 2001 that clinical inertia occurs when health care providers recognize the problem (failure to attain therapeutic targets in patients with hypertension, dyslipidemia, or diabetes) but fail to act (to initiate or intensify therapy). Clinical inertia is more than failure to act, and it has been shown that other factors such as clinician communication affect adherence. Zolnierek and DiMatteo (2009) discovered in a meta-analysis of 127 studies that the odds of adherence for patients whose physicians had been trained in communication skills were 1.62 times those of patients whose physicians did not receive communication training.[6]

Drug Therapy Nonadherence Is Common

While nonadherence is common, not all nonadherence or nonpersistence is clinically inappropriate, particularly medication discontinuation or reduction in dose as a result of medication side effects or intolerance. Nonadherence or nonpersistence associated with these causes could be misinterpreted as clinical inertia, particularly in the absence of clinical information such as in the conduct of research with administrative claims. Therefore, findings from administrative claims research cannot be used to inform about clinical inertia or therapeutic inertia without reference to clinical data such as medical chart notes about patient response to therapy including adverse effects.

We do know from research with administrative claims that nonadherence is common. For example, at 2 years of follow-up only 25% of elderly patients were adherent with statins, defined as a claim at least once every 120 days, when statins were used for primary prevention.[7] Adherence was higher at 2 years for elderly patients taking statins for secondary prevention, 36% for patients

with chronic coronary artery disease (CAD), and 40% for patients with acute coronary syndrome (ACS).[7] These findings comport with the 42% rate of adherence, defined as percent of days covered of at least 80%, with statin therapy among Medicaid and Pharmaceutical Assistance to the Aged and Disabled patients at 2 years of follow-up reported by Benner et al. (2002).[8] Brookhart et al. (2007) found that 54% of new users had a period of interruption in statin therapy for at least 90 days in the first year, but 48% of the these patients reinitiated statin therapy within 1 year and 60% within 2 years.[9] For combined therapy with statins and antihypertensives, nonadherence rates are, of course, higher; Chapman et al. (2005) found nonadherence rates of 55% at 3 months after initiation of therapy and 64% at 6 months.[10] Doshi et al. (2009) found that nonadherence with statins is high even when cost is not a factor and patients are at high risk; the rate of nonadherence with statins, measured as percent of days covered less than 80%, was 39% at 2 years of follow-up for veterans who had no cost share.[11]

A Multitude of Patient Factors Contributes to Nonadherence

When thinking of specific patient factors that might contribute to apparent nonadherence and clinical inertia, the likely suspects include medication side effects, intolerance, perception of low illness severity, or perception of a small likelihood of consequences from nonadherence.[12,13,14,15] In a follow-up of ACS patients at 3 months after hospital discharge, Melloni et al. (2009) found that 304 patients (28.2%) reported discontinuation of 1 or more recommended (evidence-based) drug therapies, and most were self-discontinuations (61.5%) that did not include provider involvement.[15] Brookhart et al. found that the strongest predictors of restarting statin therapy after a gap of 90 or more days were occurrence of MI (odds ratio [OR] = 12.2, 95% confidence interval [CI] = 8.9-16.9) and an office visit with the physician who initially prescribed the lapsed therapy (OR = 6.1, 95% CI = 5.9-6.3).[9]

Less obvious are patient lifestyle factors that have the effect of raising the bar for attainment of biomarker and other goals. Compelling data reported this year (August 2009) from the EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) survey show that despite more drug therapy, patients with coronary heart disease often do not attain blood pressure control, and almost one-half of all patients remain above target lipid levels at 6 months following a coronary artery bypass graft, percutaneous coronary intervention, or hospitalization for acute MI or ischemia.[16] The principal culprits include the usual cast of characters: smoking, obesity, and lack of exercise. In the EUROASPIRE surveys that began in 1995-1996,[17] EUROASPIRE I (n = 3,180) found that 20.3% of patients with demonstrable cardiac disease were smokers, a proportion that was unchanged in EUROASPIRE II (21.2% of 2,975 survey respondents) and in EUROASPIRE III (18.2% of 2,392 survey respondents; $P = 0.64$), and the proportion of women smokers aged less than 50 years has increased.[16] The frequency of obesity (body-mass index [BMI] of 30 kilograms per meters squared [kg per m^2] or greater) increased from 25.0% in EUROASPIRE I to 32.6% in II and 38.0% in III ($P < 0.001$). The frequency of self-reported diabetes mellitus increased from 17.4% to 20.1% and 28.0% ($P = 0.004$).

Similarly discouraging trends have been reported in King et al.'s 2009 comparison of National Health and Nutrition Examination Survey (NHANES) data for 1988-1994 versus 2001-2006.[18] Of U.S. adults aged 40-74 years, the percentage with BMI exceeding 30 kg per m^2 increased from 28% to 36%; smoking rates were unchanged at 26%-27%; and the percentage engaging in physical activity 12 times per month or more declined from 53% to 43%. Those with histories of hypertension, diabetes, or cardiovascular disease were no more likely to maintain healthy lifestyles than those without.[18] Similar results were reported in a 2006 analysis of self-reported height and weight data gathered in U.S. Behavioral Risk Factor Surveillance System surveys. The rate of obesity (BMI greater than 30 kg per m^2) increased from 15.3% in 1995 to 23.9% in 2005, a relative increase of 56%. In 2005, 61% of U.S. adults were overweight, defined as a BMI of at least 25 kg per m^2.[19]

Statistical modeling performed by Ford et al. (2007) suggests that these trends have affected cardiovascular outcomes in the United States despite increasing use of evidence-based

TABLE 1 Factors Contributing to Apparent Clinical Inertia[a]

Clinician[b]	Patient	Health System
• Failure to initiate treatment • Failure to titrate treatment to goal • Failure to set clear goals • Underestimation of patient need • Failure to identify and manage comorbid conditions such as depression • Insufficient time • Insufficient focus or emphasis on goal attainment • Reactive rather than proactive care	• Medication side effects • Too many medications • Forgetfulness • Cost of medication • Denial of disease • Denial of disease severity • Perception of low susceptibility • Absence of disease symptoms • Mistrust of clinician • Poor communication with clinician • Low health literacy • Mental illness, depression, substance abuse • Lifestyle	• No clinical guideline • No disease registry • No visit planning • No active patient outreach • No decision support • No team approach to care or lack of care coordination • Poor communication between clinician and office staff

[a]Derived in part from O'Connor et al.(2005).[4]

[b]O'Connor et al. use the term "physician factors" with occasional reference to "providers,"[4] and Phillips et al.(2001) use the terms "physicians" and "health care providers" interchangeably.[2]

therapies.[20] The model was designed to explain the decline in U.S. deaths from coronary disease from 1980-2000, using such national data sources as population estimates by age and gender from the U.S. Census Bureau, coronary heart disease-related death rates by age and gender from the National Center for Health Statistics, and data on lifestyle factors (e.g., smoking, obesity) and chronic medication use from NHANES 1976-1980 and 1999-2000.[21] Results suggested that mortality reductions attributable to use of evidence-based therapies and lifestyle improvements in smoking and physical activity were partially offset by increases in BMI and diabetes prevalence.[20]

Shifting Sands for Guidelines Based on Biomarkers

Criticism of instances of alleged clinical inertia also should be buffered by the consequences that can occur from blind adherence to clinical guidelines. Critics have argued that some clinical guidelines are little more than masquerades in which expert recommendations are influenced by payments from corporations that gain from the messages. For example, Rodney A. Hayward, a diabetes expert at the University of Michigan, and Jerome E. Groopman, professor of medicine at Harvard University, suggested that pharmaceutical companies influenced diabetes care guidelines in order to sell more glucose-lowering drugs and that clinical guidelines developed by experts influenced by corporate donations tend to recommend overtreatment in general.[22] The National Committee for Quality Assurance (NCQA) had adopted the lower-is-better philosophy for hemoglobin A1c for diabetes care. NCQA is, of course, not a small player in the matter of clinical practice guidelines because it has significant influence over the measures used by insurers in payment for performance to individual physicians and medical groups, including financial bonuses. NCQA reportedly received about $3 million, or about 10%, of its revenue in 2008 from drug and medical device makers.[22]

The lower-is-better standard for A1c ran into a paradigm-changing event with disclosure of the results at 1 year of follow-up in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. In ACCORD, the all-cause death rate was higher in the intensive-therapy group (target A1c below 6.0%; n=257) compared with the standard therapy group (target A1c from 7.0% to 7.9%; n=203; HR=1.22, 95% CI=1.01-1.46, P=0.04), equivalent to 14 deaths per 1,000 patients per year in the intensive-therapy group versus 11 per 1,000 in the standard therapy group.[23] Two other outcomes in ACCORD were unfavorable: hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P<0.001). There was no significant difference between the 2 groups in the number of patients who experienced a primary endpoint outcome (nonfatal MI, nonfatal stroke, or cardiovascular-related death).

In July 2008, NCQA announced that it would no longer assess quality of care by the measure of A1c less than 7%.[24] Observing that the lower-is-better focus on glucose control had drawn clinical attention "away from things like daily aspirin, daily statin with aggressive [low-density lipoprotein] targets, and aggressive titration toward blood-pressure targets, which have been proven to work," Dr. Darren McGuire, a cardiologist with a specialty in diabetes, lauded the change by the NCQA: "A1C <7%…never should have been included in the first place, given the paucity of clinical outcomes evidence."[24]

Similarly, our confidence in the lower-is-better philosophy has been challenged for other fundamental biomarkers, low-density lipoprotein-cholesterol (LDL-C), and blood pressure. Lower-is-better for LDL-C was challenged by the results of the ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) and ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) clinical trials that were made public in late 2007 and early 2008.[25] ILLUMINATE investigators found that despite raising high-density lipoprotein cholesterol and lowering LDL-C, treatment with the combination of torcetrapib and atorvastatin increased rates of cardiovascular events and all-cause mortality in patients at high cardiovascular risk. ENHANCE trial results indicated that greater reduction in LDL-C was *not* associated with reduced rates of thickening in carotid artery walls. In blood pressure control, Messerli et al. (2006) found in secondary analysis of the International Verapamil-Trandolapril Study (INVEST) an *increase* in the risk of the primary outcome (all-cause mortality, nonfatal MI, or nonfatal stroke) when diastolic blood pressure was less than 70 to 80 mm Hg in 22,676 clinically stable patients with CAD and hypertension.[26] In INVEST, patients were treated with sustained release (SR) verapamil or trandolapril to achieve blood pressure <140/90 mm Hg or <130/85 for patients with either diabetes or renal impairment. The researchers found that rates of the primary outcome were 31.8%, 17.4%, and 8.9% for patients with diastolic blood pressures of 60 mm Hg, >60 to 70 mm Hg, and >70 to 80 mm Hg, respectively.

This sort of finding from secondary analysis of the INVEST randomized controlled trial contributes to caveats in the full versions of most clinical guidelines. Specifically, the evidence to support targets is limited by patient nuances and other factors that make the biomarker recommendations unachievable in many patients. Unfortunately, it is likely that most clinicians read the summaries rather than the full versions of clinical guidelines, if they read them at all. Campbell and Murchie (2004) observed that new levels of "unwarranted complexity" are found in ever longer guideline documents.[27] Campbell and Murchie touched on the subject of clinical inertia without identifying it as such when they concluded that "appropriate management of blood pressure should therefore be guided by an informed dialogue between patients and doctors and not by blind pursuit of blood pressure targets."[27]

Best Practices Change—AMI-6 Was Here and Then Gone

Clinical inertia must also be evaluated in the context that evidence-based practice is a moving target. Since the evidence is constantly evolving, guidelines for evidence-based practice must be dynamic.[28] The change in the target A1c values in the clinical guidelines that was precipitated by the ACCORD trial and other evidence was dramatic, as were the questions that arose around the importance of pursuing lower-is-better for LDL-C following dissemination of the results from ILLUMINATE and ENHANCE. Equally significant was the abandonment of the AMI-6 (acute myocardial infarction patients without beta-blocker contraindications who received a beta-blocker within 24 hours after hospital arrival) by the Centers for Medicare & Medicaid Services (CMS), effective April 1, 2009. After 4 years of touting the administration of beta-blockers at hospital admission for acute MI patients as a quality of care standard in its "pay-for-reporting" program in the Medicare prospective payment system, CMS announced on December 31, 2008, that it was "retiring" AMI-6.[29] This about-face by CMS is of great importance because reporting is required of hospitals to avoid financial penalties and because the CMS action marked for the first time the removal of a quality measure outside of the customary rule-making process that is required by Medicare statute.[30]

Actually, CMS was late to abandon AMI-6, since the evidence supporting beta-blocker administration on hospital admission for most acute MI patients changed in 2005, culminating with publication of the ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT). COMMIT researchers found that patients randomized to intravenous metoprolol within 24 hours of onset of a suspected MI were less likely than control patients to experience reinfarction (2.0% vs. 2.5%, respectively, $P=0.001$) and ventricular fibrillation (2.5% vs. 3.0%, respectively, $P=0.001$) but more likely to experience cardiogenic shock (5.0% vs. 3.9%, respectively, $P=0.001$).[31] The American College of Cardiology and the American Heart Association deleted this measure from their clinical guidelines and performance measures in December 2007.[32] There is understandable uncertainty about best practice for at least some clinicians as such benchmarks undergo revision or rescission.

Titration to Biomarker Goals—A Fool's Errand?

Perhaps the productivity of pursuing lower-is-better biomarker levels is undermined by the imperfect or at least incomplete nature of present biomarkers. There is a large need in chronic care and disease management research to recognize the limitations of the biomarker measures themselves and the potential unreliability of individual biomarker values. For example, there is a growing literature about the importance of inflammation in predicting intermediate and endpoint outcomes, such as the report by Pradhan et al. (2009), which showed that the inflammatory biomarker high-sensitivity C-reactive protein remained elevated and at similar levels across treatment groups in patients with type 2 diabetes treated with metformin, placebo, or insulin plus metformin and placebo, despite differential effects on glucose control.[33]

Keenan et al. (2009) reminded us that titration to biomarker goals should be informed by the potential unreliability of individual readings.[34] The PeRindopril prOtection aGainst Recurrent Stroke Study (PROGRESS) was a randomized controlled trial performed in 172 centers in Asia, Australasia, and Europe. Keenan et al.'s evaluation of mercury sphygmomanometer measurements of blood pressure in the PROGRESS trial showed a high probability of false-positive blood pressure readings.[34] For example, the ratios of false-positive increases in systolic blood pressure were 6 false-positive increases in systolic blood pressure for every true increase of more than 10 mm Hg. The ratios for false-positive increases in diastolic blood pressure were 39 for every true increase of 10 mm Hg and 3.5 for every true increase of 5 mm Hg. The likelihood of false-positive blood pressure readings was higher with shorter time intervals between readings.

Adherence to Best Practice Guidelines Does Not Guarantee Outcomes

Realistic expectations about the results of adherence to clinical practice guidelines are also called for when considering the subject of possible clinical inertia. The Asthma Control Evaluation Study (ACES) involved 546 inner-city residents aged 12 through 20 years with persistent asthma who were evaluated over 46 weeks during which optimal asthma management based on guidelines "was offered."[35] The authors of ACES found "little predictive power" for various measures typically used to predict future asthma activity among patients highly adherent to anti-asthmatic therapies and being treated using clinical guidelines. The measurements of asthma activity in ACES included the fraction of exhaled nitric oxide in parts per billion, total immunoglobulin E (IgE), allergen-specific IgE, allergen skin test reactivity, asthma symptoms, lung function, peripheral blood eosinophils, and, for some patients, airway hyper-responsiveness and sputum eosinophils. These measures were found to account for 11.4% of future maximum symptom days and 12.6% of exacerbations. Maximum symptom days were predicted "to a modest extent" by symptoms, albuterol use, and previous exacerbations, while future exacerbations were "somewhat" predicted by asthma symptoms, albuterol use, previous exacerbations, and lung function.

Appropriate Use of the Label "Clinical Inertia"

Evidence concerning clinical inertia is continually evolving, and it is becoming increasingly difficult and will soon be impossible to sift through the clutter in order to cull out the high-quality evidence. In 2007, the National Library of Medicine processed over 670,000 new citations, bringing its archive to 16 million references,[36] and the pace continued in 2008 with about 60,000 new citations per month from 5,319 medical journals or an annual volume of about 720,000 new articles per year.[37] Still, clinical

inertia does exist in some form and deserves investigation and dissection. For example, Shah et al. (2005) hypothesized that specialists (endocrinologists, geriatricians, or internists) might be less prone to clinical inertia in diabetes care compared with primary care physicians.[38] Perhaps this is not surprising, but Shah et al. documented that specialists were more likely (45.1% of patients) to intensify antidiabetic drug therapy among elderly patients with A1c values greater than 8% compared with 37.4% of patients who received care from primary care physicians ($P=0.009$).[38] Noteworthy for managed care, of the many factors examined by Shah et al., policies restricting formulary access to newer, more expensive medications did not appear to contribute to clinical inertia.

The medication nonadherence siren song has been fueled in the last 2 years by the seemingly omnipresent push sponsored by the pharmaceutical industry to convince us that lower prescription drug copayments are necessary, commonly labeled today as valued-based insurance design (VBID).[39] While the recent report "Thinking Outside the Pillbox" (August 2009), also trumpeted the now-familiar song, there was recognition of the need for a systemwide approach to improving medication adherence in patients with chronic disease, citing factors such as the patient's inability to navigate the health care system, cognitive impairment, and imperfect drug regimens.[40] We may indeed be stuck with some authors using the term "therapeutic inertia," but we suggest that when this term is used that authors be specific and not attribute failure of patients to meet therapeutic goals solely to clinicians' failure to intensify treatment in a timely manner. There is more than enough blame to go around, including patient factors such as forgetfulness and real-world impediments such as precipitation of side effects from intensifying drug therapy. And, the modifier "apparent" is warranted when using the terms "clinical inertia" or "therapeutic inertia," since almost no research is conducted with all of the clinical data, including patient interviews and complete medical records, necessary to paint unsuccessful disease management with the brush of "clinical inertia."

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