Lyndra White Paper on Adherence to Medication

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C. Everett Koop, the former U.S. Surgeon General, famously said, “Drugs don’t work in people who don’t take them.” Although this is self-evident, it was stimulated by what has been called, “America’s other drug problem” (National Council on Patient Information and Education, 2013). An alarming percentage of people do not, in fact, take their medications as directed. The National Council on Patient Information and Education (2013) estimates that 50-60% of medications to treat chronic disease are not taken as prescribed. Between 20% and 30% of prescriptions are never even filled (Tamblyn et al., 2014), even after patients suffer a serious event. For example, 27% of patients discharged from the hospital after a myocardial infarction did not fill their prescriptions within 7 days of discharge (Jackevicius et al., 2008), and less than half of patients with coronary artery disease adhere to their post-MI-secondary prevention medications within the year following an acute MI (Benner, 2002). Adherence is a problem for many common diseases. In a study of 700,000 adults, the percentages of patients, by diagnosis, who were adherent, defined as a medication-possession ratio (MPR) of at least 80%, over the first year of therapy were 72.3% for hypertension, 68.4% for hypothyroidism, 65.4% for type 2 diabetes, 60.8% for seizure disorders, 54.6% for hypercholesterolemia, 51.2% for osteoporosis, and 36.8% for gout (Briesacher et al., 2008).

Taking medication is a complex behavior that occurs over time, and failures at different stages represent different forms of non-adherence. Primary non-adherence occurs when a patient never fills a prescription, secondary non-adherence when a patient does not consistently carry out the prescribed therapy as intended, and non-persistence when a patient completely discontinues therapy. All three forms can impair treatment outcomes. Typically, discussion of non-adherence focuses on patients who take less than the prescribed amount of a medication, but patients who take more than the prescribed amount are also non-adherent. Not following prescribed directions for taking medication increases the risk of drug-drug interactions and other medication errors.

Patients’ non-adherence to medication regimens has two major consequences. First, it contributes to unnecessary disease progression, complications, reduced functional abilities, and reduced quality of

life. This is especially true for medications that have a narrow therapeutic range, as missed doses can result in sub-therapeutic levels and extra doses in toxicity. Among 2175 patients in the Beta Blocker Heart Attack Trial, those with poor adherence (<75% of prescribed therapy) had a 2.5-3.1-fold increased risk of death within 1-year compared to patients with better adherence (Desai and Choudhry, 2013). Non-adherent patients with diabetes have higher blood pressures, HgbA1c, and LDL levels, as well as higher rates of all-cause hospitalization and mortality (Ho et al., 2006). The World Health Organization (2003) observed that, "more health benefits worldwide would result from improving adherence to existing treatments than by developing new medical treatments."

The second major consequence of non-adherence is increased costs to the health care system. Coleman et al., (2012) estimated that 33-69% of medication-related hospital admissions are the result of poor medication adherence. Jha et al. (2012) estimated that approximately 700,000 emergency room visits and 340,000 hospitalizations could be avoided annually if non-adherent patients with diabetes were adherent. This would represent a savings of $4.68 billion annually. Adding the savings from eliminating loss of medication persistence, which occurs in 25% of patients, brings the total to $8.3 billion for this one disease alone. Siris et al. (2006) estimated that increasing adherence to therapy for osteoporosis would result in 300,000 fewer fractures each year, which would represent a savings of approximately $3 billion in the US. Estimates of the total costs of non-adherence vary depending on the assumptions made, but they are high. For example, the New England HealthCare Institute (2009) puts this figure at $289 billion (summing all outcomes resulting from non-adherence, including total physician visits, total hospital admissions, total emergency department visits, total long-term care facility admissions, and total additional prescriptions).

Improving adherence would reduce these costs. The Congressional Budget Office (2012) estimated that a 1% increase in the number of prescriptions filled would produce a 0.2% decrease in spending on other medical services such as emergency room visits and hospitalizations. This might be a substantial underestimate. Roebuck (2014) analyzed data from a large cohort of elderly patients with one or more of four chronic diseases (congestive heart failure, hypertension, diabetes, dyslipidemia) that account for 40% of Medicare Part D utilization. The cost offsets varied by illness, but estimates for all 4 diseases were 3 to 6 times greater than the CBO estimate. In a systematic review of the impact of

adherence on coronary artery disease costs and outcomes, Bitton et al. (2013) found that high adherence to medication reduced the annual costs for secondary prevention of coronary artery disease between $294 and $868 per patient. This represented a 10.1% to 17.8% cost reduction between the low and high adherence groups. They also estimated that each dollar spent improving adherence to prescribed therapies would reduce overall medical costs by $7 for diabetic patients, $5 for hypercholesterolemic patients, and $4 for hypertensive patients (WHO, 2003).

Adherence in Neuropsychiatric Diseases

To adhere to a regimen, a patient must i) accept and understand the need for the medication and the prescribed regimen, ii) accurately execute the regimen, and iii) persist with it over time. This requires cognitive skills, including verbal memory, working memory, reasoning, and planning and organization. It is not surprising that patient adherence varies and may be particularly challenging in patients with neuropsychiatric disease.

Dementia. Cognitive impairment is a predictor of poor adherence (Okuno et al. 2001). Two weeks after hospital discharge, patients with dementia had 2-3-fold increased risk of taking either more than 30% less or more than 20% more of the prescribed medication (Gray et al., 2001). Among patients with Alzheimer's Disease (AD), the 1-year discontinuation rate for cholinesterase inhibitors ranged from 40% to 65%, with up to 90% stopping after 2 to 3 years (Maxwell et al., 2014). In an Austrian study of treatment-naïve dementia patients, after 6 months on therapy, 34% had stopped taking the medication prescribed (cholinesterase inhibitor or NMDA receptor antagonist) at 6 months and 58.5% at one year. Only 39% of patients had a MPR >80% during the first 6 months, and 34% during the 12 months of the study (Haider et al., 2014).

Cognitively impaired patients often have other chronic diseases for which they must take medication and adherence to these is often poor as well. For example, Rattinger et al. (2012) found that patients with AD and related disorders had lower adherence to medications for congestive heart failure than patients without AD. Poor adherence in patients taking multiple medications places them at increased risk of adverse side effects and drug-drug interactions.

There are many barriers to achieving good adherence in patients with dementia. Regimens are often complex involving multiple medications. Patients often have poor insight into their disease and the

need for medications and have difficulty understanding new and complex directions. Other risk factors include living alone in the community, lack of social supports, poor communication with the prescribers, overestimation of self-efficacy, depression, problem drinking, lack of transportation to access medication and health care, and limited financial means (Hudani and Rojas-Fernandez, 2015; Saleh et al., 2013). Many patients require the assistance of a caregiver to manage their medications, often a spouse or other family member. Adherence can suffer if the caregiver, such as an elderly spouse, also suffers from some cognitive impairment and poor health literacy (Campbell et al., 2012).

The most important factors identified in studies of strategies to increase adherence are less frequent dosing interval regimens, and close monitoring, including directly observed therapy (Campbell et al., 2012)

Schizophrenia. Systematic reviews indicate that patients with psychosis take less than 60% of the recommended amount of their anti-psychotic medication, 41% do not regularly take the medication as directed, prescription completion rates vary widely (28% to 85%), and that rates of irregular medication use range from 31% to 62% (Tiihonen et al., 2011). The problem appears to be greater among Medicaid patients, as in one study only 12% of patients with schizophrenia completed a full year of uninterrupted treatment (McCombs et al., 1999).

A variety of factors have been identified as contributing to non-adherence among patients with schizophrenia. Among the most important are lack of insight and illness awareness (Novick et al., 2015 BMC Psychiatry). Other patient-related factors include substance abuse (Colizzi et al., 2016) and the belief that the medication is no longer needed. Among treatment-related factors are a lack of efficacy of the medication and the adverse side effects. Given the nature of psychotic illness, a variety of psychosocial factors also affect adherence, including the quality of the therapeutic relationship between the patient and the clinician, family and social support, and social engagement of the patient.

The consequences of non-adherence include hospitalization and longer stays, suicide, violence, substance abuse, criminal behavior, and greater use of emergency psychiatric services (Higashi et al., 2013). In analyses of 35,815 psychotic patients, Marcus and Olfson (2008) found that 12% of acute care inpatient admissions and 13% of inpatient days could be attributed to patients not taking anti-psychotic medications. A 5-year study of patients with first-episode psychosis indicated that stopping medication

increased the relapse rate two-fold (Robinson et al., 1999). Using pharmacy data, Vallenstein et al. (2002) found that patients with an MPR less than 0.8 had a rate of psychiatric admission that was 2.4 times greater than that of patients with an MPR near 1 and, once admitted, had longer hospital stays. A ratio greater than 1 was also associated with an increased risk of admission. In one study (Law et al., 2008), a two-fold increase in the odds of re-hospitalization was seen in patients with a gap of only 10 days in receipt of atypical antipsychotics (Weiden et al., 2004). This is most likely due to the relatively short half-lives of these agents.

Adherence rates vary by medication. The availability of depot formulations of the first generation antipsychotic agents, providing medication release over a period of weeks, appears to reduce the impacts associated with non-adherence in patients with psychotic disorders. In the analyses of Tiihonen et al. (2006), patients who received perphenazine depot had the lowest risk of discontinuation and re-hospitalization. Because it is likely patients with a history of poor adherence are given depot injections, this study likely underestimates the magnitude of the benefit. Systematic reviews suggest a non-adherence rate of 24% associated with depot injections (Young et al., 1999), while Shi et al. (2007) found a mean medication possession ratio of 91% for patients receiving depot first generation antipsychotics. However, variations in adherence persist among different patient groups even with depot injections. Olfson et al. (2007) found that only 10% of Medicaid patients in California continued treatment past 6 months.

SSRI/SNRI and antidepressants. The evidence is remarkably consistent that approximately half of patients with major depression will not be taking a prescribed medication 3 months after beginning therapy (Osterberg and Blaschke, 2005). For example, among 44,000 patients in a commercial administrative claims database, adherence (MPR $\geq$0.8 and no treatment gap exceeding 15 days) ranged from 25.5% to 38.1% for all SSRIs (Liu et al., 2011). In another study of 14,933 patients with depression, PTSD, or social anxiety disorder, adherence over a 40- month period was less than 27% regardless of the medication prescribed (paroxetine, sertraline, citalopram) (Giannetti, 2004). In 45,481 patients in a reimbursement claims database, persistence with SSRIs (renewing prescription within 30 days) decreased from 95.5% at 1 month, to 52.6% at 2 months, 37.6% at 3 months, and 18.9% at 6 months (Ereshefsky et al., 2010). In an Italian study, out of nearly 350,000 SSRI/SNRI treatment episodes, only 23.8% were

adherent during a 6-month follow-up period, defined as treatment duration ≥120 days, prescription coverage >80%, and gaps between prescriptions <3 months (Poluzzi et al., 2013). This pattern is independent of the age of the patient. In adolescents with treatment-resistant depression, 50.8% were non-adherent by clinician pill count (Woldu et al., 2011). In patients ≥65 years, the overall rate of non-adherence to paroxetine therapy (MPR<80% over 180 days, no gap >15 days before 90 days of therapy) was 62.7% (Keene et al., 2005).

Adherence is lower in patients with comorbid pain conditions (Wang et al., 2011), alcohol or drug dependence (Liu et al., 2011). Patients with depression are also up to 3 times more likely to be non-adherent to medications prescribed to treat chronic comorbid medical conditions. There is some evidence that adherence and persistence for anti-depressant therapy are greater when the dose is titrated. This might be why adherence to a controlled release formulation of paroxetine is somewhat better (45.0%) than to the immediate release formulation (35.6%) (Keene et al., 2005). Side effects, a major factor in patients' discontinuation of anti-depressant therapy, are often less severe with controlled release formulations, presumably because of lower peak plasma drug concentrations. The complexity of the regimen also affects adherence, as patients are less adherent to antidepressant combinations than to monotherapies (Warden et al., 2014).

The impact of non-adherence to anti-depressant therapy on health care costs is not clear. There is evidence that adherence to anti-depressant therapy is associated with lower medical costs, but the total direct costs are similar (Stein et al., 2006; Cantrell et al., 2006). Because depression is a risk factor for patient non-adherence to therapies for comorbid conditions, accounting for the indirect costs associated with these comorbid conditions increases the cost of non-adherence. For example, from a claims data base, Katon et al. (2005) found that the 40% of patients who were adherent to anti-depressant medication were twice as likely to be adherent to medications for comorbid conditions (coronary artery disease, dyslipidemia, diabetes mellitus). However, patients were less adherent to antidepressant medication than to comorbid disease medications. Furthermore, patients who were adherent to anti-depressant therapy had lower total medical charges, ranging from 6.4% to nearly 20% lower, depending on the comorbid condition. Much of the savings were due to reductions in inpatient and outpatient medical charges.

Adherence in chronic medical diseases

Statins. Non-adherence is sometimes reported to be a greater problem for medications that are prescribed for chronic asymptomatic conditions. Presumably this is because patients feel well and do not perceive any benefits. Statins prescribed to treat dyslipidemia are an example of this. Skipping one or even multiple consecutive doses can be tolerated, in contrast to some medications, such as warfarin, where minor deviations from the regimen can be life-threatening.

In patients who were hospitalized for acute coronary syndrome, 40% were adherent to statins two years later, compared to 36.1% of patients with chronic coronary artery disease not admitted to hospital, and 25.4% for patients with no known history of coronary disease being treated for primary prevention (Benner et al., 2002). In a study of more than 200,000 patients, 53% had a period of non-adherence to statins lasting 90 or more days (Brookhart et al., 2007). Age has an inverted U-shaped relationship to adherence to statin therapy, with the lowest adherence in the young and the old (Mann et al., 2010). Lower adherence has been reported in females, minorities, lower income patients, and those with comorbidities. Adherence to statins (>80% use) is associated with improved outcomes and decreased overall health care costs, compared to patients whose adherence is in the range of 60%-70% (Pittman et al., 2011).

Osteoporosis. As with most diseases, more than half of patients prescribed medication for osteoporosis stop treatment within the first year (Seeman et al., 2007; Siris et al., 2009). In a Dutch study, adherence to oral medications initially was high but more than half the patients were non-persistent within 1 year and 78% of the patients who were non-persistent did not restart or switch to other treatments within the following 18 months (Netelenbos et al., 2011).

Fracture risk is strongly associated with adherence. Siris et al. (2006) found that there is no treatment benefit if the MPR is below 50%, but that the benefit increases sharply as MPR rises above this value. Cotte et al. (2008) suggested that an MPR of at least 68% provides optimal protection against fracture. In a Belgian study, the relative reduction in risk of hip fracture was 60% for women who were persistent with bisphosphonate compared to those who were not persistent. Each incremental decrease of 1% in compliance, as measured by MPR, increased the risk of hip fracture by 0.4% (Rabenda et al., 2008). Siris et al. (2006) reported that patients who were persistent over 24 months had a 20% to 45% reduction in fracture risk compared to patients who were not persistent. In the Netherlands (Penning-van

Beest et al., 2008) patients who had an MPR ≤80% for bisphosphonate use had a 45% greater fracture risk, and patients with an MPR <20% had an 80% greater risk, compared to patients with MPR ≥90%.

The evidence is consistent in indicating that the adherence among osteoporosis patients varies with the treatment regimen. Specifically, adherence increases as dosing interval increases. Mean MPRs over 1 year in patients receiving daily, weekly, and monthly bisphosphonate therapy were 38.6%, 70.6%, and 77.7%, respectively (Kishimoto et al., 2015). Compared to daily therapy, weekly therapy was associated with better persistence over 8 years. Similar findings have been reported by Cotte et al. (2010) and Gold et al. (2007). In post-menopausal women, the mean MPR was 84.5% in women receiving medication monthly and 79.4% in women receiving medication weekly. Persistence rates over 6-months were 57.3% and 45.7% in the monthly and weekly cohorts, respectively. However, 12-month persistence rates were still suboptimal in both groups: 47.5% for the monthly cohort and 30.4% for the weekly cohort. Two-thirds (65.8%) of the patients in the weekly cohort had an MPR≥80 versus 74.1% of the patients the monthly cohort. Incident fractures were more frequent in the weekly cohort as well (6.3% versus 2.0%). In a Spanish study, the 1-year persistence was 3-5 fold greater among patients receiving monthly ibandronate or risedronate than among patients receiving daily treatment with these same medications (Carbonell-Abella et al., 2015).

Dosing regimens and adherence

The evidence is clear that regimen factors, particularly dose frequency, affects adherence. For most diseases, with the exception of respiratory/pulmonary disease, greater dosing frequency was associated with poorer adherence, with the evidence being particularly strong for diabetes, hypertension, and HIV/AIDS (Ingersoll and Cohen, 2008). In a systematic review of 51 studies that measured the adherence of patients with chronic diseases using electronic measurement, Coleman et al. (2012) found that adherence, defined in a variety of ways, was greater for a once-daily regimen than for 2, 3, or 4 times daily regimens. Furthermore, in osteoporosis treatment, 12-month persistence is greater for monthly than weekly therapy (Cotte et al., 2010).

The number of medications is another important factor. In Medicare patients, adherence fell by 28% when 2 additional prescription medications were added to the regimen of already adherent patients (Chapman et al., 2008). However, Choudhry et al. (2011) found that patients whose treatment regimen is

more “consolidated” (i.e., requiring fewer trips to pharmacy to fill prescriptions) are more likely to be adherent.

Increasing adherence

A variety of interventions have been shown to increase adherence in RCTs, but most are resource-intensive. For example, Arlt et al. (2008) provide a list of almost two dozen adherence-promoting interventions for dementia patients (Table II). In general, interventions focus on improving patient education, providing increased access of patients to clinicians, and promoting better communication between clinician and patient. Lingler et al. (2016) reported that home- and telephone-based contacts by a nurse or social worker improved adherence in patients with memory loss. For patients with HIV/AIDS, cognitive-behavioral interventions have produced more than 95% adherence to HAART in more than 90% of patients, but this was not sustained after withdrawal of the intervention (Osterberg and Blaschke, 2005). Only about half of studies find that the interventions are helpful in the HIV/AIDS population. A variety of other approaches have been suggested, including sending reminders via cellphone or PDA, and providing pillboxes with paging systems.

In the case of neuropsychiatric illnesses, efforts to improve adherence often require the engagement of family and other caregivers, cognitive-supportive interventions, and reinforcement techniques. For elderly patients, an important step in improving adherence would be early detection of impaired cognitive function, adding to the burden on primary care providers.

Eliminating or reducing patient co-pays for medication would likely be an effective strategy for increasing adherence. Among patients discharged following an MI on statins, beta-blockers, ACE inhibitors, angiotensin-receptor blockers, the percentage who were adherent was 4 to 6 points higher in the full-coverage group than in the usual coverage group (Choudhry et al., 2011). A difference was also seen in a quasi-experimental study of veterans use of lipid-lowering medications before and after a copayment increase (Doshi et al., 2009). Patients not subject at all to the increase had greater adherence and were less likely to have a treatment gap ≥90 days. Among patients with employer-sponsored insurance, a doubling of copayments resulted in a 34% reduction in use of lipid-lowering agents and a 26% reduction in the use of anti-hypertension medications (Goldman et al., 2007). In the FREEE trial, patients were randomly assigned to full prescription coverage or usual formulary coverage. Assignment to

full coverage increased rates of adherence to all preventative medications and reduced patient out-of-pocket spending for drugs, without increasing overall health expenditures (Kulik et al., 2013). Co-payment reduction, by itself, is only a partial solution, however, as less than half of patients in the trial were fully adherent to their prescribed therapies.

Non-adherence is a multifactorial problem for which there is no simple fix. Among the factors that contribute are provider-patient communication (misunderstanding of disease, complexity of target regimen, implications of deviations from regimen), a patient's interaction with the health care system (access to care, medication costs), and the provider's interaction with the health care system (knowledge of relative drug costs, insurance coverages) (Osterberg and Blaschke, 2005). Ingersoll and Cohen (2008) noted that "…the intervention most likely to result in optimal adherence for the greatest number of patients is simplification of the medication regimen [and] [P]harmacological companies should be encouraged to develop combination medications that reduce overall pill burden and regimen complexity, as well as extended-release formulations of existing efficacious medications to allow reduced dosing" (p. 221-2).

Studies of psychosis and osteoporosis strongly suggest that patient adherence to treatment regimens is increased when medication dosing intervals are longer. Daily dose is superior to multiple doses per day, weekly is superior to daily, and monthly is superior to weekly. To the extent that formulations that allow for longer dosing intervals can be developed for medications for more diseases, similar to the depot formulations of first generation anti-psychotics, it is reasonable to assume that this would result in better patient adherence to treatment regimens for these diseases.

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