

**The  
Underwriting Implications  
of  
Rx Nonadherence**

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 Milliman

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## **Preface**

Pharmacy records (Rx profiles) are one of the fastest growing underwriting assets in history.

In 2007 42% of life insurers used them.

Four years later their use had escalated dramatically to 77% and it is doubtlessly much greater today in 2013.

The most touted aspect of Rx profile protective value is pinpointing the use of “yellow” and “red” drugs by individuals who fail to disclose this information at the time they apply for coverage.

This paper looks at a different way in which these reports confer substantial value in risk appraisal.

Based on a comprehensive review of the medical literature, we will demonstrate the profound insurability implications of Rx nonadherence.

Hopefully, readers will see that this vital component of pharmacy records needs to be consistently factored into our assessments of applicants with chronic diseases.

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June 10, 2013

## Background and Concepts

### **What are the major implications of Rx nonadherence?**

*“The National Council on Patient Information and Education has aptly termed medication nonadherence America’s other drug problem.”*

Jeannie K. Lee, PharmD, et al  
Walter Reed Hospital  
*Journal of the American Medical Association*  
296(2006):2563

*“Nearly three in four Americans fail to follow their doctor’s instructions for taking prescription drugs, a problem that is associated with 125,000 deaths each year according to the National Consumers League.”*

Varun Vaidya, PhD, et al  
University of Toledo College of Pharmacy  
*Patient Preferences and Adherence*  
7(2013):21

*“Adherence rates vary considerably across disease conditions and treatment regimens, and can be quite low even for treatments that are highly effective.”*

M. Robin DiMatteo, PhD, et al  
University of California-Riverside  
*Medical Care*  
45(2007):521

*“Lack of adherence is a major barrier to achieving treatment goals for individuals with chronic health conditions.”*

John F. Steiner, MD, MPH, et al  
Kaiser Permanente Colorado  
*Annals of Internal Medicine*  
157(2012):580

*“...if unrecognized, poor compliance can be mistaken for treatment failure and can lead to inappropriate dosage changes or unnecessary treatment changes.”*

M. Alan Brookhart, PhD, et al  
Harvard University Medical School  
*American Journal of Medicine*  
120(2007):251

According to the World Health Organization:

*“Increasing the effectiveness of adherence preventions may have a far greater impact on the health of the population than any improvements in specific medical treatments.”*

Zachary A. Marcum, PharmD  
University of Pittsburgh Medical School  
*Journal of the American Medical Association*  
309(2013):2105[editorial]

Clearly, Rx nonadherence is a major issue in both healthcare and risk appraisal.

### **What is adherence?**

*“Medication adherence refers to the extent to which patients take medications in the manner prescribed by their physicians. For the most part, the term ‘adherence’ has replaced the term ‘compliance’ in the medical literature.”*

Ian M. Kronish et al  
Columbia University Medical School  
*Progress in Cardiovascular Disease*  
55(2013):S90

Medication adherence consists of two elements: compliance and persistence. Compliance is taking medication as intended and persistence is maintenance of medication use over time. [Roumie]

Adherence encompasses both of these concepts. [Kothawala]

### **What clinical benchmark is used most often to define Rx nonadherence?**

Failure to take a medication at least 80% of the time [Lachaine]

### **Does partial adherence matter?**

*“Evidence is overwhelming that, as a group, those with partial concordance [adherence] as well as those with nonconcordance have inferior health outcomes.”*

Alex J. Mitchell, MB, MSC, et al  
Leicester General Hospital, UK  
*Journal of Clinical Pharmacology*  
26(2006):109[editorial]

### **What is the difference between primary vs. secondary nonadherence?**

Primary nonadherence is the failure to fill a prescription. Secondary nonadherence is when the patient fails to take the drug as prescribed. [Kronish]

From an underwriting perspective, primary nonadherence probably confers a somewhat greater overall risk than secondary nonadherence.

The only viable clue we have to primary nonadherence is when there is reference by the applicant or in his medical records that a drug was prescribed, but that drug is not reported in the Rx profile. This is not foolproof, however, because the applicant may have paid in cash or the prescription was not recorded in the pharmacy report due to some other mechanism.

Our most reliable sources of evidence of secondary nonadherence are pharmacy records based on drug claims data reflecting medication refills. This is regarded as an “accurate and objective measure” of Rx adherence in clinical medicine. [Pedan]

### **How prevalent is secondary nonadherence overall?**

*“Studies have consistently shown that...approximately 50% of medications for chronic disease are not taken as prescribed.”*

Meera Viswanathan, PhD, et al  
University of North Carolina Medical School  
*Annals of Internal Medicine*  
157(2012):785

This is a broad generalization. As you will see, secondary nonadherence rates vary widely within and across drug classes.

### **When does secondary nonadherence first manifest?**

Typically within 6 months after filling a prescription the first time. [Agarwal, Chapman and Benner, Perreault and Lamarre, Serna]

### **Is intentional versus non-intentional adherence distinguished clinically?**

Yes, because different mechanisms are operative and one goal of physicians is to find ways to enhance adherence. [Cervený, Gadkari, Lehane, Osterberg]

***Is this distinction relevant in underwriting?***

No.

Our concerns are the prevalence, risk factors and consequences of nonadherence, independent of whether it occurred for intentionally or unintentionally.

***What are some of the overall factors associated with nonadherence that have implications for risk assessment and insurability?***

- Most studies show that adherent patients have superior clinical outcomes. [Boswell]
- Rx adherence in chronic disease is associated with significantly more days at work and lower disability rates. [Carls]
- Between 33% and 69% of medication-related hospital admissions have been linked to Rx nonadherence. [Mulhem]
- Nonadherence is more common in asymptomatic chronic diseases. [Krousel-Wood]
- Adherence to drug delivery using a transdermal patch is substantially greater than when the same drug is administered orally. [Cohen, Molinuevo]
- Nonadherence frequently leads to inappropriate intensification of treatment. [Whooley]
- The capacity of physicians to recognize patient nonadherence is described as “generally poor.” [Kane, Smith]
- Patients often exaggerate their adherence when questioned by their physician. [Kothawala]
- Patients are more likely to be adherent if the medication is prescribed by a specialist as compared to their primary care doctor. [Krymchantowski]
- The vast majority of patients over age 65 cannot name all of the medications they currently take. [Makaryus]
- Rx refill rates by Medicare patients are substantially higher than in other insurance-based contexts. [Kennedy]

## **RED FLAGS for Rx Nonadherence**

### **What is the #1 RED FLAG for nonadherence to medication use?**

Depression – encompassing clinical diagnosed mood disorders as well as the presence of multiple depression symptoms in the absence of a clinical diagnosis. [Davis and Jandrisevits, Demyttenaere and Adelin, Gonzalez, Magai, Willemen]

*“...among every 100 noncompliant patients, on average 63.5 can be expected to be depressed as compared to 36.5 not depressed.”*

M. Robin DiMatteo, PhD, et al  
Op. Cit.

*“...it is more likely that depression increases mortality through specific mechanisms such as noncompliance with medical treatment than through specific biological mechanisms affecting cardiovascular disease risk.”*

Sylvia Wassertheil-Smoller, PhD, et al  
Albert Einstein School of Medicine  
*Archives of Internal Medicine*  
165(2005):119[letter]

In a 31-study metaanalysis, Grenard and coworkers reported that depressed patients were 1.8 times more likely to be nonadherent than patients free of this condition.

### **Why are depressed individuals prone to nonadherence?**

*“Overall, about half of depressed individuals believe they can stop their antidepressants as soon as they begin to feel better and that drugs can be taken as required.”*

Alex J. Mitchell, MB, MSC, et al  
Op. Cit.

### **What are the other recognized RED FLAGS and YELLOW FLAGS for overall Rx nonadherence in the clinical literature?**

Please see Table One.

**Table One: Overall Risk Factors for Rx Nonadherence**

**RED FLAGS**

- Major and/or persistent adverse side effects
- Cigarette smoking
- Psychiatric disorders
- “Type D” personality
- Living alone
- Lack of social support
- Cognitive dysfunction
- ADL and IADL deficits
- Substance abuse history
- Polypharmacy (taking 5 or more medications daily)
- Not keeping medical appointments
- Not having recommended medical tests
- Not wearing seat belts
- “Fair” or poor” self-rated health

**YELLOW FLAGS**

- Age 35 and under
- Age 70 and over
- Divorced, separated or widowed
- Less than 12 years of formal education
- Low income
- Taking multiple daily doses
- Fear of side effects
- Frequent business travel
- Negative perceptions about the drug or the need for taking it
- Heavy use of potent pain-killing drugs
- Severe insomnia and other sleep disorders

[Badangarav, Aghabekyan, Blackburn, Bosworth, Bryson, Claxton, Coleman, DiMatteo, Gadkari, Glombiewski, Kronish, Lamba, Marcum, Marengo, McHenry, Medic, Molloy, Natarajan, Nielsen, Osterberg, Reach, Rolnick, Saini, Schoenthaler, Sockalingam, Tsai, Williams]

Underwriters using pharmacy records are well served by checking refill rates when applicants have one **RED FLAG** or two **YELLOW FLAG** risk factors.

## Nonadherence in Hypertension

*“Despite the availability of effective therapy, hypertension remains poorly controlled in the United States and other industrialized countries.... Patient compliance with prescribed treatments is a central reason for the failure to control hypertension in those receiving therapy.”*

Phillip S. Wang, MD, DrPH, et al  
Harvard University Medical School  
*Journal of General Internal Medicine*  
17(2002):504

According to a 2013 CDC report, the prevalence of high blood pressure overall as well as hypertension on Rx is steadily increasing. [JAMA. 309(2013:1986)]

Most insurers will issue some portion of treated hypertensive applicants on a preferred (and sometimes even super-preferred) basis, potentially on the sole basis of having “normal” readings on a current paramedical.

Compliance with the guidelines for proper blood pressure measurement cited by American Heart Association is a major challenge in a mobile paramedical setting. This raises concern for the adequacy of these blood pressure readings as a basis for offering preferred coverage to applicants on treatment and thereby makes the matter of medication adherence all the more important.

### **What is the #1 reason for poor control of high blood pressure despite ostensibly adequate Rx?**

Nonadherence. [Ram]

*“Poor adherence to antihypertensive drugs has been acknowledged as a major contributor to the lack of blood pressure control, which in turn significantly affects clinical outcomes.”*

Lia Gentil, MD, et al  
University of Sherbrooke, Quebec  
*Journal of the American Geriatric Association*  
70(2012):2297

### **How common is Rx nonadherence in patients with high blood pressure?**

In a 44,167-patient cohort at Kaiser Permanente, overall nonadherence ranged from 17%

to 28% across subsets of patients. [Adams]

Among 18,806 newly diagnosed hypertensive subjects, 51% were nonadherent after 6 months. Acute CV events were 40% fewer in those who did adhere to treatment. [Mazzaglia]

Other studies show nonadherence rates from 35% to 83% after 1-2 years, depending primarily on how nonadherence was measured. [Bailey, Butler, Caetano]

***Do we have any data on primary nonadherence in hypertension?***

Yes.

It was 15.6% in one study and 25% in another. This means that as many as one in four persons given antihypertensive Rx never fill their prescription! [Cooke, Lagu]

***What is the main reason adherence to blood pressure drugs is so low?***

Lack of symptoms – hypertension rarely presents with symptoms recognized by the patient as being due to their high blood pressure. [Marshall]

***What are the other clues to nonadherence specifically associated with antihypertensive Rx?***

- Comorbid psychiatric diagnosis
- Age 35 or younger
- Cigarette smoking
- Borderline readings at the time Rx is prescribed
- Obesity
- Substance abuse
- Multiple adverse life events
- Sedentary lifestyle
- Taking more than one pill or taking pills more than once a day
- Being sole or primary caregiver for a terminally ill family member
- Lack of social support
- Poor self-perceived health

[Adams, Bailey, Bramley, Cooke, Gentil, Holt and Muntner, Irvin, Krousel-Wood, Lee, Wang]

As you see, many but not all **RED FLAGS** for Rx nonadherence with blood pressure medication are the same as those linked to overall nonadherence in chronic disease patients (as shown in Table One).

***Is poor adherence with antihypertensive Rx a significant risk factor for excess mortality?***

Yes, based on a new 5-year follow-up study of 218,047 patients. [Wong]

## Nonadherence with Statins

*“Despite the well-established benefits and abundance of clinical management guidelines strongly advocating statin use in high-risk cardiac conditions, long-term adherence to statin regimens in patients who are appropriate candidates has generally been poor, and continued use of statins drops substantially over time.”*

Joel A. Lardizabal, MD, et al  
University of California-San Francisco Medical School  
Vascular Health and Risk Management  
6(2010):843

In addition to high-risk conditions, statins are widely prescribed to patients with chronic circulatory and other diseases who have relatively normal lipid readings.

And the number of statin users continues to increase.

Just as in treated hypertension, insurance applicants who are prescribed statins are deemed eligible for preferred risk status.

### **How extensive is statin nonadherence?**

- In 962,877 subjects followed for 6 years, 46% became nonadherent over time. [Yang]
- In a Canadian study of 115,290 patients over the same interval, 38% were eventually nonadherent (and the cost of medication is considerably lower in Canada). [Perreault]
- In a province-wide investigation in Saskatchewan, nearly half of persons prescribed statins did not adhere to their use. [Evans]
- Among 14,257 statin “users” in the New Jersey Blue Cross system, 64% were less than fully adherent. [Chan]

Mann and coworkers did a systematic review of statin adherence and found that it was U-shaped, with middle-aged patients showing superior adherence rates compared to younger and elderly individuals.

Statin adherence among insurance applicants is likely somewhat better than in the general public.

For example, a recent investigation of applicants at one insurer found that 72% were

adherent based on the criteria of filling at least 80% of prescriptions. [Whitmore, personal communication 5/13/13]

***Why is early nonadherence in statin therapy particularly significant?***

Because it takes 6 to 12 months before the benefits of treatment become apparent, according to the National Cholesterol Education Program.

Nonadherence is the #1 reason statin users do not achieve their goal in terms of lowering LDL-C and the main reason for Rx intensification in hypercholesterolemia. [Calip, Martin, Pittman, Pladewell]

Nonadherence is also significantly greater when statins are used for primary prevention (patients without CV events) than in secondary prevention (patients that had MIs and other CV events). This is consistent with the fact that asymptomatic individuals are less prone to take medication. [Foody, Lemstra, Naderi]

***Is there any correlation between interim cholesterol readings after initiating statin therapy and the likelihood of nonadherence?***

Yes, according to a brand new study.

Mann and Glazer found that the greater the variance between interim cholesterol readings, the higher the probability that the patient is nonadherent.

Thus, widely differing readings are suspicious whereas a consistent pattern of favorable cholesterol levels minimizes the odds that the individual is not taking the statin as prescribed.

**Even if current cholesterol and other lipid readings happen to satisfy your preferred criteria, it is essential to look for interim readings on the APS and to routinely check the refill record before granting preferred coverage.**

***What else is important about statin nonadherence?***

Nonadherence to statins has been shown to result in:

- 20% greater incidence of hospitalization due to coronary disease. [Corrao]
- 25% higher risk of deep venous thrombosis. [Rabinowich]

- Overall increased rate of adverse clinical outcomes. [Patrick]
- 1/3rd greater likelihood of workplace and motor vehicle accidents. [Dormuth]
- Fewer follow-up visits to personal physicians. [Lemstra]
- Lesser probabilities of having recommended eye examinations, screening for fecal occult blood and PSA tests, and compliance with routine bone densitometry for osteoporosis [Dormuth]

These reports demonstrate the insidious implications associated with not taking statins as prescribed.

***Is there an association between statin nonadherence and excess mortality?***

As expected, yes.

- In a review of 10 prospective studies, all-cause mortality was 45% lower in adherent vs. nonadherent patients. [Simpson]
- In a new clinical outcomes analysis, all-cause mortality was 40% less in patients with high statin adherence. [Degli Esposti]
- In a Finnish investigation, the adjusted hazard ratio for all-cause mortality was 2.7-fold greater on subjects nonadherent to statin Rx. [Allonen]

**Bottom line: there are substantial insurability implications associated with nonadherence to statin drugs.**

## Nonadherence in Cardiovascular Disease

*"In patients with heart disease, poor adherence to prescribed medications is common and is associated with increased mortality and rehospitalization."*

Nina Rieckmann, PhD, et al  
*Journal of the American College of Cardiology*  
48(2006):2218

*"Applying the overall nonadherence rates from our study [376,162 patients on CV Rx]...nonadherence leads to approximately 130,000 avoidable deaths in the United States"*

Sayed H. Naderi, MD, et al  
Queen Mary Hospital, London  
*American Journal of Medicine*  
125(2012):882

### **What is the #1 risk factor for nonadherence in patients with circulatory disease?**

Depression – it is also one of the major risk factors for excess shorter duration mortality in these cases. [Dempe, Hawkins, Song, Rieckmann, Tang]

### **What are the extent and implications of nonadherence in heart attack survivors?**

Primary nonadherence was 18% in post-MI patients and as high as 30% following revascularization procedures. [Hlatky, Jackevicius, Rushworth]

Secondary nonadherence ranged from 21% to 35% in four investigations. [Aghabekyan, Kassab, Martin, Zhang]

Decker et al found that nonadherers were 58% more likely to experience interim angina within the first year after discharge.

Martin and coworkers reported that post-MI Rx nonadherence is a **RED FLAG** for also not participating in cardiac rehabilitation.

### **Which drugs are typically prescribed to heart attack survivors? [Bauer]**

- Aspirin
- Clopidogrel
- Statins
- Beta-blockers or calcium channel blockers
- ACE inhibitors or angiotensin receptor blockers

**What are the ranges of nonadherence rates to these drugs in patients with CV disease, based on clinical studies?**

Drug Class	Nonadherence After 1 Year
Aspirin	29% to 57%
Beta-blockers	29% to 57%
Calcium channel blockers	28% (one study)
Statins	26% to 59%
ACE inhibitors	22% to 55%
Clopidogrel	13% to 33%

[Ho, Newby, Robinson, Roughead, Sanfelix-Gimeno, Schulman]

**How does nonadherence to these drugs impact all-cause mortality?**

The only study we could find focused on three of these drugs: [Ho]

Drug Class	All-Cause Mortality Hazard Ratio
Statins	1.9
ACE inhibitors	1.7
Beta-blockers	1.5

**What are the implications of nonadherence to Rx after a coronary event?**

*“Adequate adherence...has been linked to fewer cardiac events and increased survival in patients with acute coronary syndrome (ACS).”*

Leah K. Bauer, MD, et al  
Harvard University Medical School  
*American Journal of Cardiology*  
109(2012):1266

***What do we know about nonadherence in other circulatory disease contexts?***

- A 10% increase in nonadherence to antiarrhythmic drugs has been linked to a 3-fold greater risk of arrhythmia-induced death. [Obias-Manno]
- Specifically with the antiarrhythmic amiodarone, all-cause mortality in nonadherent patients was 2.3 times higher than in those who took this potent drug as advised. [Irvine]
- In a Canadian study of patients given warfarin (Coumadin) for atrial fibrillation, 9% did not fill their prescription and 32% of those who did were nevertheless nonadherent within 12 months. [Gomes]
- Nonadherence in 10 studies of patients taking digitalis for heart failure and/or atrial fibrillation was 43% in outpatients and 25% after hospital discharge. [Kongkaew]
- Disease-related hospitalizations are twice as frequent in nonadhering patients with congestive heart failure. [Fitzgerald]
- Post-stroke nonadherence is 30% with statins and 16% with antithrombotic agents. [Hohmann]
- Stroke patients with PTSD are 3 times more likely to not adhere to Rx as prescribed than those free of this common stroke comorbidity. [Kronish and Edmundson]

**It is clear from these studies that there is substantial mortality due to pharmaceutical nonadherence in applicants with a history of cardiac and other circulatory events.**

**Rx refill data should always be referenced in these cases.**

## Rx Nonadherence in Diabetics

*“Failure to follow treatment recommendations is reported as a serious and widespread problem in type-2 diabetes and believed to lead to diabetic complications such as blindness, poor wound healing, neuropathy and kidney failure.”*

Richard L. Nahin, MD, et al  
National Institutes of Health  
*BMC Complementary and Alternative Medicine*  
12(2012):193

### **What are primary nonadherence rates in T2DM?**

They range from 3% to 31% in three studies. [Fischer, Shah and Hirsch, Shin]

### **What are overall secondary nonadherence rates in T2DM?**

Between 37% and 51% in six studies. [Bailey and Kodack, Cramer, Egede, Hertz, Rolnick, Simoni-Wastila]

In addition, 2-year nonadherence to insulin in Swedish type-1 diabetics was almost 50% [Nielsen]

### **Do physicians usually assess Rx adherence on diabetic patients?**

*“Medication nonadherence is common and often not directly assessed by clinicians...clinicians may attribute poor glycemic control to therapeutic ineffectiveness and may increase the dosage of current medications or add medications to the regimen.”*

P. Michael Ho, MD, PhD, et al  
*Archives of Internal Medicine*  
166(2006):1836

### **What are the main RED FLAGS for nonadherence in diabetics?**

- Polypharmacy (taking 5 or more drugs)

- Depression
- Age 35 and under
- Poor social support
- Heavy drinking
- Multiple comorbid conditions
- Visual complications
- Missed appointments for diabetic care
- Residing in a rural vs. urban area
- Weight gain
- Taking an alpha-glucosidase inhibitor such as acarbose

[Bailey and Kodack, Cox, Currie, Egede, Hauber, Hertz, Malmenas, Odegard, Tiv]

***Is Rx nonadherence a major factor in failing to achieve adequate control of blood glucose (HbA1-c)?***

Actually, it is well documented as the #1 reason.

[Aikens, Alvarez-Guisasola, Bezie, Bogner, Currie, Grant, Hillary, Lawrence, Nagrebetsky, Raum, Rhee]

- Kindmalm and coworkers found that 31% of T2DM patients on insulin were nonadherent and their mean HbA1-c was significantly higher (7.3%) than that of patients who were Rx-adherent (6.6%).
- Krapek et al reported that mean HbA1-c was 10% lower in adherent diabetics.

**The first factor we need to consider when diabetic applicants exhibit poor control is potential nonadherence as reflected in Rx refill records.**

***Are diabetics generally more compliant in other aspects of their care?***

No. [Rudnicki]

Care Component	% Nonadherent
Routine Foot Exams	45%
Annual Flu Vaccine	48%
Daily Glucose Self-monitoring	60%

### ***What is significant to insurability regarding adherence in diabetics?***

- Good adherence reduces the risk of CV events 39%. [Zeber]
- Diet compliance lowers the CV event risk 44%. [Zeber]
- T2DM Rx nonadherence is the #2 adherence-related reason for hospitalization after depression. [Senst]
- Diabetics who self-monitor their glucose have substantially higher Rx adherence rates. [Virdi]
- Nonadherence to statins among diabetics was 63% after one year in a 2011 study. [Wu]
- Nonadherence to neuropathic pain medication in diabetics with neuropathy is 25% – despite relatively severe symptoms. [Oladapo]

### ***Is nonadherence a significant mortality consideration in diabetics?***

Yes.

It has been shown to be a major factor in both mortality and morbidity. [Pladevall, Sokol]

- Rothenbacher et al found that nonadherence in T2DM was associated with 2.7-fold greater 1-year mortality.
- Currie and Peyrot reported that among 2946 type-1 diabetics followed for 30 months, all-cause mortality was 1.6 times higher in those who either did not take medication as prescribed or missed diabetes-related MD appointments.
- In a different paper on the same study, the magnitude of the excess mortality linked to missing appointments or not taking medication as indicated was essentially the same as that found in diabetic smokers or those with nephropathy. [Currie]

**The spectrum of consequences linked to nonadherent behaviors involves both failing to take medication and of other adverse patterns of behavior. All of these should be considered when assessing the insurability of diabetic applicants.**

## Nonadherence in Psychiatric Disorders

*“...poor adherence to psychotropic medication may contribute in myriad ways to the substantial morbidity and mortality associated with many medical conditions.”*

Robert H Howland, MD  
*Journal of Psychosocial Nursing*  
45(2007):15

### **What is the overall nonadherence rate with antidepressants?**

A 14-study review showed a median nonadherence rate of 40%. However, this paper was published in 2002 and recent findings are a tad less favorable. [Pampallona]

In a 7525-subject 2010 paper, 56% were nonadherent after just 4 months. [Serna]

Two others show nonadherence rates of 46% and 50% at 6 months. [Lu and Roughead, Wang and Liu]

Clearly, antidepressant nonadherence rivals that of any drug class.

### **What else is significant about antidepressant nonadherence?**

- Most depressed patients who stop their Rx do not tell their attending physician they did so. [Demyttenaere]
- Nonadherence with monoamine oxidase inhibitors (third-line antidepressants) was 87% in 6 months; the highest of any antidepressant drug class. [Sheehan]
- Patients with relapsed/recurrent depression who were nonadherent during the first episode are likely to repeat the same behavior. [Simon]
- Rx nonadherence is – improbably, one might say – greater when patients also get outpatient psychotherapy. [Wessels]
- In a huge study, nonadherence was markedly more common when depressed patients were treated in primary care as opposed to by psychiatrists. [Robinson and Long]

### **What do we know about nonadherence rates in other psychiatric disorders?**

- The odds of not adequately taking Rx range from 47% to 63% in bipolar disorder. [Bates, Berger, Sajatovic]
- Nonadherence in adult ADHD has been reported to be as high as 43%. [Caisley]
- In obsessive-compulsive disorder, Rx nonadherence was 63% and adherence to participation in cognitive behavior psychotherapy was 51%. [Santana]
- Overall nonadherence in social anxiety disorder was 81%. [Lim]
- Nonadherence is high in inpatient schizophrenics and failure to take Rx is the #1 reason for relapse in psychosis. [Addington, Caseiro, Malla]

**Bottom line: nonadherence to Rx and other treatment is notoriously high in patients with a wide range of psychiatric disorders. We need to routinely check the refill behavior of all persons prescribed psychotropic drugs.**

***Are there risk factors for nonadherence in psychiatric disorders that are especially prominent in a mental illness context?***

Yes.

- Females < age 40
- Onset > age 65
- Comorbid personality disorders
- Substance abuse disorders
- > 3 recurrences of the disorder
- Higher education attainment – *which is the opposite of what we find in most other Rx nonadherence contexts*
- Frequent employment changes
- Positive family history
- Suicidal ideation

[Akerblad, Bates, Belli, Gau, Kronish and Edmundson, Montes, Sajatovic, van Servellen]

## Nonadherence in Chronic Lung Disease

### **What is the Rx nonadherence rate in COPD?**

It ranges from 30% to 60%. [Agh, Cecere, Khmour, Neugaard, Qian, Restrepo]

### **What are the RED FLAGS for COPD nonadherence?**

For the most part, they are similar to those for other drugs.

Current smoking is the #1 **RED FLAGS** overall.

Others include:

- Younger age at diagnosis
- Major depression
- Rx used > 3 times daily
- Asymptomatic or having only mild symptoms

[Agh, Cecere, Restrepo]

### **What else is significant regarding nonadherence in COPD from an underwriter's perspective?**

- Nonadherence substantially increases the frequency of exacerbations and hospitalizations. [Heisler, Simoni-Wastila]
- Nonadherence to pulmonary rehabilitation is 60% [Hayton]
- Markers for rehab non-participation are current smoking, more hospital admissions and lower BMI. [Sabit]

### **What is the nonadherence rate in adult asthma?**

At least 30% in clinical studies. [Rolnick]

In a survey of 573 asthmatic patients, 85% said they were nonadherent to Rx use on some basis. [De Smet]

***Is nonadherence greater in pediatric asthma?***

Yes – it ranges from 57% to 85%. [Elkout, Valdya]

It is also more common in patients using inhaled steroids as compared to beta-agonists and other prominent asthma drugs. [Ahmedani, Murphy]

This is significant because failing to use low-dose inhaled steroids increases the risk of symptom exacerbation by 2.4-fold. [Rank]

Murphy and coworkers reported that nonadherence in severe asthma predictably led to high eosinophil counts, lower FEV-1 and more frequent need for ventilation therapy...all of which are consistent with worst case risks.

Interestingly, one recent study found that the #1 reason asthmatics were nonadherent – by self-admission – was *“if I have no symptoms, I don’t have asthma.”* [Sofianou]

***Are asthmatics adherent to allergen immunotherapy?***

Not according to a new study of 6468 patients, where 82% no longer complied by the third year of therapy. [Kiel]

## Nonadherence in Other Prevalent Disorders

### ***What do we know about the prevalence of Rx nonadherence in inflammatory bowel disease (IBD), consisting of ulcerative colitis and Crohn disease?***

Overall Rx nonadherence was 21% and 45% in two literature reviews. [Jackson, Latakos]

- After just 12 months, between 72% and 80% of patients on 5-ASA drugs as maintenance therapy failed to take this medication as prescribed. [Mitra, Yen]
- Ulcerative colitis patients adherent to 5-ASAs have 31% fewer hospitalizations and 34% fewer emergency department visits. [Mitra]
- In a new Scandinavian study, 52% of patients discontinued infliximab or adalimumab after 11 months of therapy. [Riis]
- Overall, nonadherence increases the risk of clinical relapse more than 2-fold. [Kawakami, Khan]

### ***Are there Rx adherence issues in systemic lupus erythematosus (SLE)?***

Yes.

Overall Rx nonadherence is 38%. [Marengo]

It is higher with hydroxyurea than with prednisone or immunosuppressives. [Koneru, Marengo, Ting]

### ***What are the main risk factors and RED FLAGS for nonadherence in this potentially lethal disease?***

- The two main factors are depression and cognitive dysfunction, which are both associated with a highly unfavorable prognosis in SLE.
- Being single.
- Having comorbid illnesses that also need medication.
- Increasing MD and emergency care visits.
- Symptom flare-ups .

[Chambers, Julian, Koneru, Mosley-Williams]

### ***Is nonadherence a concern in chronic hepatitis?***

Yes.

For chronic hepatitis B, it ranges from 8% to 34%, and low adherence increased the odds of viral breakthrough 10-fold. [Chotiyaputta, Chotiyaputta and Hongthanakorn, Lieveld]

In HBV, nonadherence was the main cause of treatment failure (just as we know it is in hypertension). [Ha]

### ***How about chronic hepatitis C?***

In a study of 16,043 U.S. veterans treated for chronic HCV, only 22.5% were adherent to their drug protocol over the course of therapy. The drivers of nonadherence were depression (which is often induced or exacerbated by taking interferon), substance abuse, pretreatment anemia and comorbid CAD. [Butt]

### ***What is the risk of nonadherence in epileptics?***

Between 41% and 58% in three studies. [Carpentier, Davis, Modi]

Davis and colleagues found that nonadherence correlated with a substantial increase in emergency care visits and inpatient admissions, both associated with high-risk cases in underwriting.

Ridsdale et al showed that Rx nonadherence increased mortality 80%, which was the same mortality impact as alcohol abuse in this study.

### ***Is Rx nonadherence an underwriting concern in multiple sclerosis or osteoporosis?***

It should be for MS, with rates being between 12% and 59% in 26 studies. [Bischoff, Margolis, Menzin]

Nonadherent MS patients had higher rates of relapse, inpatient/emergency care and disability progression [Menzin, Steinberg]

In osteoporosis:

- Primary nonadherence is 30% [Reynolds]

- In a million-patient study, nonadherence with bisphosphonate osteoporosis Rx – after just 1 year – ranged from 65% with risedronate to 33% with zoledronate. [Ziller]
- Even when medication was changed due to patient concerns, 12-month nonadherence was still over 40%. [Ward]
- Adherence is associated with two key advantages of concern to underwriters: 30% lower incidence of hip fracture and 23% lower risk of osteoporotic fractures at all sites. [Olsen]

***What are the reported nonadherence rates in other disorders?***

- Parkinson disease: 46% to 61%. [Daley, Davis and Edin, Richy]
- Chronic non-cancer pain: 57% by self-admission and as high as 66% with duloxetine and 87% with pregabalin [Markotic, Zhao] It was also found that cigarette smokers overuse pain Rx in this context! [Broekmans]
- Proton pump inhibitor (PPI) Rx in patients with Barrett esophagus: 67% at 12 months. [El-Serag]
- Warfarin (Coumadin) for deep venous thrombosis (DVT): 77%, with a 60% greater risk of a second DVT. [Chen]
- Antibiotics for bacterial pharyngitis/pneumonia: 58%. [Llor]
- Overactive bladder: between 43% and 83% in 30 days. [Sexton]
- Topical Rx in psoriasis: 40% to 75% in 23 studies. [Devaux, Kivelevitch]
- Cyclosporine for severe psoriasis: 56%. [Swimberghe]
- Duloxetine in fibromyalgia: 66%. [Cui]
- Daily tadalafil for erectile dysfunction: 52%. [Buvat]
- Patch or gum for smoking cessation: under 50% after just 4 weeks. [Ferguson]

**These investigations in diverse impairments demonstrate that nonadherence is likely quite prevalent in most chronic diseases as well as at least some acute care scenarios.**

## Nonadherence in Breast Cancer

This is becoming an increasingly important issue now that American experts are recommending greater use of tamoxifen and other drugs used for the same purposes. [*British Medical Journal*. 346(2013):6]

Tamoxifen is used in three different contexts:

1. Treating hormone receptor-positive patients with localized or metastatic breast cancer.
2. Reducing the rate of recurrence and future invasive disease in patients with breast carcinoma in situ.
3. Lowering the risk of breast cancer in high-risk women.

**The underwriter must know the context in which tamoxifen has been prescribed as the risk implications differ substantially between these three groups.**

### ***What are the nonadherence rates for tamoxifen?***

Over 3 to 5 year therapy, they range from 21% to 73% based on the criteria for nonadherence and the context of use. [Gotay, Kahn, Lash, Nekhlyudov, Owusu, Partridge, Wigertz]

In one study consisting solely of women with early invasive breast cancer, nonadherence was only 7% after 1 year and 16% at 3 years. Those who were nonadherent had a higher rate of interim breast cancer events. [Dezenti]

Finnish oncologists reported a 3-fold greater risk of breast cancer recurrence over 2 years in patients prescribed tamoxifen that were nonadherent. [Markkula]

### ***How does adherence differ with regard to the aromatase inhibitor drugs also used in breast cancer management?***

In three studies, nonadherence ranged from 18% to 38% over 3 years and then jumped to 60% in year 4 and thereafter. [Fontein, Hershman, Neuget]

### ***Are there any RED FLAGS for nonadherence to tamoxifen and aromatase inhibitors?***

Yes.

- Nonadherence is most common in premenopausal women and women age 75 and over.
- It is more likely in unmarried women.
- In one study, the #1 predictor of nonadherence was taking antidepressant medication.
- Predictably, smokers and heavier drinkers are less compliant.
- In patients with known breast cancer, BMI < 25 is an indicator of a higher probability of nonadherence.

As noted above, adherence trails off after several years. This is significant because new protocols either extend therapy beyond 3-5 years or change drugs after the first has been administered for a number of years.

[Barron, Fontein, Hershman, Lin, Markkula, Wigertz]

## Nonadherence in Life-Threatening Conditions

One would logically expect Rx and other forms of treatment adherence to be highest in persons having life-threatening diseases.

Unfortunately, the following evidence argues that this expectation is flawed.

- Nonadherence to antiretroviral drugs in HIV patients was 31% in a 2005 study. [Bouhnik]
- In chronic myeloid leukemia, 20-26% of patients failed to take outpatient oral chemotherapy drugs as advised. [Guerin]
- Breast and colon cancer patients with advanced disease were nonadherent to the drug capecitabine in 23% of cases. [Bhattacharya]
- While this finding may be counterintuitive, nonadherence to cancer pain medication has been shown to be as high as 59%. [Valeberg]
- Among patients with spasticity sequelae from strokes, spinal cord injuries and other mechanisms, compliance with the drugs baclofen and tizanidine was under 50%. [Halpern]
- In studies of organ transplantation patients nonadherence to post-transplant immunosuppressive Rx ranged from 22% to 73%. [Berquist, Chisholm-Burns, Lieber, Lamb, Stilley]
- In heart transplants performed on young adults, 28% did not comply with immunosuppressives. [Wray]
- 80% failed to fully comply with mandated care prior to autologous stem cell transplantation, and the dominant reason was depression. [Mumby]
- After hematologic stem cell transplantation, Khara et al noted that 25% did not take Rx as prescribed.
- Even dialysis patients exhibit high levels of nonadherence to various forms of treatment. Most of these patients are single, male, smokers and have less formal education. [Iborra-Molto, Kugler]

**Most of the disorders cited above would not be candidates for life insurance. They were included here to make the point that we cannot simply assume Rx adherence, and therefore need to pay close attention to whatever evidence we have in this regard on all substandard cases.**

## **Nonadherence in the Elderly**

Older age business has grown substantially in our market. Many companies write a major portion of their new business on elders. It is arguably the most complicated domain of medical underwriting.

In the words of a clinical geriatrician:

*“Medication noncompliance...leads to increased hospital admissions and accounts for a substantial number of medical emergencies in this population.”*

Nancy Lutwak, MD  
New York University Medical School  
*Clinical Geriatrics*  
June, 2012:34

Butler et al discovered that Rx nonadherence was responsible for between 4% and 11% of geriatric hospital admissions and 8% of elder emergency care visits.

### ***Does Rx nonadherence in elders significantly impact mortality overall?***

Yes.

In one study it increased all-cause mortality 24% overall and 55% when nonadherence was judged to be unintentional. [Vik]

### ***What are the overall medication nonadherence rates in elders?***

- In a 139-study literature review, it was 37%. [Cramer and Benedict]
- In a survey of chronic disease patients  $\geq$  age 75, self-admitted nonadherence was 25% after just 4 weeks. [Barber]
- Fallis reported 25% primary nonadherence and 24% 30-day secondary nonadherence to various drugs in patients of a primary care center.

### ***What about nonadherence in elders by drug class?***

- In a Quebec investigation, 2-year nonadherence to blood pressure medication was

41%, while in a US study at Ochsner Clinic it was 55%. [Gentil, Krousel-Wood]

- Elder nonadherence to statins was 75% after 5 years and almost 60% over a shorter time interval. [Brenner, Swindle]
- In a study of elders taking both blood pressure and lipid medications, 67% did not adhere to one or both after 12 months of treatment. [Chapman]
- The nonadherence rate for elders on SSRI antidepressants was 64%, as compared to 55% under age 65. [Akerblad]

These data tell us that nonadherence is generally higher overall at age 65 and over.

**What RED FLAGS are most prevalent for nonadherence in elders?**

- Depression is #1
- Complex dosing
- Polypharmacy
- Lower cognitive test scores
- ADL deficits
- Lack of social support/living alone
- Not seeing physicians as advised
- “Fair” to “poor” self-rated health

[Bolkan, Carney, Corsonello, Gellad, Gentil, Holt, Kennedy, Mansur, Shah, Stoehr, Suzuki, Thiruchselvan, Wroth]

**Most of these are RED FLAGS in a general underwriting context. Nearly all are independent predictors of excess mortality at older ages.**

## **The Placebo Effect and the Implications of Complementary and Alternative Medicine (CAM)**

### **What is the “placebo effect”?**

*“The placebo effect can be defined as a psychophysiologic effect that is derived from expecting a benefit from treatment. Laboratory studies have shown that the receipt of placebo medications can result in demonstrable biological effects.”*

Ian M Kronish, MD  
Op. Cit.

### **What are the implications of the placebo effect?**

*“In trials for prevention of coronary artery disease, individuals who complied poorly with placebo had worse health outcomes than those who were compliant, suggesting that inherent characteristics in poor compliers increase morbidity. Differences in lifestyle partly explain this finding.”*

Juliet E. Compston and Ego Seeman  
Cambridge University  
*The Lancet*  
368(2006):973[editorial]

*“There were no significant differences in the risk ratio of response to active therapy versus placebo between patients enrolled in antidepressant...trials.”*

Marlene P. Freeman, MD, et al  
Massachusetts General Hospital  
*Journal of Clinical Psychology*  
71(2010):682

Experts maintain that the health advantages inherent in the placebo effect are largely related to diverse favorable health behaviors and practices. [Hartz]

***Do we have objective evidence of the favorable impact of the placebo effect, supporting the argument that nonadherence to placebo may be as significant as nonadherence to medication in some settings?***

Yes.

Simpson and coworkers looked at the association between adherence to both placebo and medication in terms of mortality in 21 studies encompassing 46,847 subjects. There was no essential difference between medication and placebo:

Overall Mortality Risk	
<b>Nonadherence</b>	1.00
<b>Good adherence</b>	
Medication	0.55
Placebo	0.56

Other studies have shown significant cardiac and cancer risk advantages accruing to placebo-adherent individuals. [Avins, Hartz, Padula]

***Does use of complementary and alternative medicine (CAM) adversely impact medication adherence?***

We found six studies addressing this issue, and all but one of them showed no adverse impact on Rx adherence in patients who used various CAM remedies. [Chambers, Gohar, Holt, Laba, Weizman, Wutoh]

While this aspect of CAM use has no adverse implications for insurability, underwriters need to be alert to CAM use in patients with serious diseases.

For example, Nahin and his National Institutes of Health colleagues discovered the following when looking at CAM use in diabetics.

Their data show the adjusted odds ratio for being an active CAM user in terms of various adverse diabetic history factors:

	Adjusted Odds Ratio
Diabetes duration $\geq$ 10 years	1.7
3 or more comorbid illnesses	1.7
Functional limitations	1.7
Kidney disease	1.5
Severe vision impairment	1.5
At least 3 adverse risk factors	1.9

**These revelations underscore the importance of asking about CAM use – especially herbs and other digestibles – routinely during teleinterview drilldowns of applicants with major impairments.**

## **Epilogue: Nonadherence in Other Contexts and the Healthy Adherer Effect**

### **Cancer Screening**

#### ***How common is nonadherence to recommended mammographic screening?***

Even in clinically significant circumstances, it typically exceeds 50% [Lu, Rahman]

In one study nonusers of mammography had 3-fold greater breast cancer mortality than users, whether or not their malignancy was discovered mammographically. [McCarthy]

#### ***Do most high-risk patients advised to have screening colonoscopy comply with this recommendation?***

No. Between 33% and 60% did not have a colonoscopy in three studies. [Hudson, Lukin, Myong]

Similarly, nonadherence to followup Pap tests after a prior positive test is also greater than one would expect (33% to 56%) in this context. [Melnikow, Rojas]

#### ***What are the markers for nonadherence to recommended cancer screening in high-risk patients?***

- Negative family history
- Age < 40 or > 70
- Less than 12 years of formal education
- Multiple unrelated comorbid disorders

[Armelaio, Lu, Rahman]

### **Continuous Positive Airway Pressure (CPAP)**

We included CPAP adherence in obstructive sleep apnea (OSA) because it is an excellent example of the implications of nonadherence in a form of treatment other than medication.

#### ***What is the overall nonadherence rate with CPAP in OSA?***

38%. [Gagnadoux, Galetke, Keller, Madbouly]

**Has any dominant risk factor for CPAP nonadherence been identified?**

Besides functional issues related to having to wear the face mask while sleeping, the chief predictor of nonadherence is major depression. [Sanchez]

This further underscores the insidious association between depression and nonadherence in diverse therapeutic contexts.

**Why is CPAP adherence such a significant issue in OSA management?**

It is the #1 predictor of whether symptoms are effectively managed. [Campos-Rodriguez, Marin]

In a new study the dominant risk factor for cardiovascular mortality in OSA patients was CPAP use:

Hazard Ratios for CV Mortality		
	CPAP Use	
	Adherent	Nonadherent
Mild/Moderate OSA	0.19	1.60
Severe OSA	0.55	3.50

This study illustrates the formidable impact of CPAP nonadherence in the underwriting of obstructive sleep apnea.

**What else do we know about nonadherence in contexts other than medication?**

- 42% of patients presenting with chest pain and were advised to have a treadmill stress test declined to do so. [Milano]
- Only 52% of patients seen in the emergency department and told to consult their personal physician for further care related to the medical problem at hand...actually saw their own MD as advised. [Naderi and Barnett]
- At-risk patients advised to have screening for osteoporosis were 35% more likely to decline if they had a serious medical disorder and 50% less disposed to have such screening when their self-rated health was “fair” or “poor.” [Ryder]
- In a study of 15,984 type-2 diabetics, missing 2 or more followup appointments was linked to 61% higher mortality when compared to those who did not miss any appointments. [Currie]

- In patients with HIV infection, missed appointments correlated with an 8-fold higher mortality risk. [Colubi]

**All of these reports underscore the profound insurability implications of nonadherence to medical care in contexts other than medical therapy.**

## **Healthy Adherer Effect**

*“A sustained high level of adherence identifies a pattern of healthy behaviors.”*

Ross J. Simpson, MD, PhD  
University of North Carolina Medical School  
*Journal of the American Medical Association*  
296(2006):2614[editorial]

*“...patients who are more adherent to drug treatment take better care of themselves by engaging in various behaviors aimed at improving and maintaining health.”*

Colin R. Dormuth, ScD, et al  
University of British Columbia School of Medicine  
*Circulation*  
119(2009):2051

### **What is meant by the “healthy adherer effect”?**

We would define it as engaging in a constellation of practices and behaviors associated with good health to the extent that these choices increase longevity and reduce morbidity.

These behaviors and practices often impact mortality independent of clinical history and conventional risk factors.

Over the last decade, the research supporting this concept has increased dramatically and it is widely recognized in epidemiology, public health and clinical medicine as a valid and relevant entity.

### **Which behaviors and practices have been shown to contribute to the healthy adherer effect?**

This is a partial list. No doubt there are others that should be included:

- Not smoking tobacco or discontinuing the habit
- Eating a healthy and balanced diet with modest intake of red meat, saturated fats, salt, etc.
- Engaging in hobbies and pastimes involving physical activity
- Engaging in a regular pattern of exercise
- Having a personal physician
- Keeping medical appointments
- Following physicians' advice, such as adhering to home monitoring of glucose if diabetic or home monitoring of blood pressure if hypertensive
- Wearing a seat belt
- Having a favorable driving record
- Having routine health screening as advised
- Getting annual flu shots, especially at age 65 and over
- Averaging between 6 and 9 hours of sleep per night
- Having a network of family members and friends with whom one interacts often and in a positive manner
- Temperate alcohol intake
- Use of dietary supplements
- Participation in rehabilitative programs in the wake of illnesses and injuries
- Pet ownership, particularly in the elderly

[Chapman, Coups, Nash, Glazer, Hartz, Hayton, Karter, Schectman, Schueler, Sharp, Vyas, Wu and Zhu]

## Closing Observations

The evidence presented in this paper supports the following conclusions:

1. Nonadherence to pharmaceutical therapy is disturbingly high in most prevalent medical conditions.
2. This is true for patients with serious and even life-threatening diseases.
3. Nonadherence is associated with a wide range of substantial adverse outcomes.
4. The most consistent #1 nonadherence risk factor is depression.
5. Underwriters should routinely assess Rx adherence in all applicants taking **RED** and **YELLOW** drugs.
6. There are **RED FLAGS** for Rx nonadherence that should encourage underwriters to pay particularly close attention to evidence of nonadherence.
7. Nonadherence to physician advice, as well as to recommended screening and treatment in non-pharmaceutical contexts, is also a major risk assessment issue.
8. Adherence is part of a constellation of favorable behaviors and practices known as the “healthy adherer effect” that has major implications for insurability, independent of medical history. Insurers should consider adding at least some of these behaviors to teleinterview scripts.

## References

- Adams. *JAMA Internal Medicine*. 173(2013):54
- Addington. *Psychiatric Services*. E-published 1/1/13
- Agarwal. *American Journal of Therapy*. 16(2009):119
- Agh. *Respiration*. 82(2011):328
- Aghabekyan. *Journal of Interventional Cardiology*. 25(2012):469
- Ahmedani. *Annals of Allergy and Asthma Immunology*. 110(2013):75
- Aikens. *Diabetes Medicine*. 30(2013):338
- Akerblad. *Patient Preferences and Adherence*. 2(2008):379
- Allonen. *Clinical Cardiology*. 35(2012):E22
- Alvarez-Guisasola. *Diabetes, Obesity and Metabolism*. 10, Supplement 1(2008):25
- Armelaio. *Endoscopy*. 42(2010):15
- Avins. *Journal of General Internal Medicine*. 25(2010):1275
- Badangarav. *Mayo Clinic Proceedings*. 81(2006):1009[editorial]
- Bailey. *American Journal of Medical Science*. E-published 8/9/12
- Bailey and Kodack. *International Journal of Clinical Practice*. 65(2011):314
- Barber. *Quality and Safety in Health Care*. 13(2004):172
- Barron. *Cancer*. 109(2007):832
- Bates. *Primary Care Companion: Journal of Clinical Psychiatry*. 12(2010):pii
- Bauer. *European Journal of Cardiovascular Prevention and Rehabilitation*. 17(2010):576
- Belli. *Journal of Clinical Psychopharmacology*. 27(2007):412[letter]
- Benner. *Journal of the American Medical Association*. 288(2002):455
- Berger. *BMC Psychiatry*. 12(2012):99
- Berquist. *Pediatric Transplantation*. 10(2006):304
- Bezie. *Diabetology and Metabolic Syndrome*. 32(2006):611
- Bhattacharya. *Journal of Oncology and Clinical Practice*. 18(2012):333
- Bischoff. *Journal of Neurology*. 259(2012):2347
- Blackburn. *Canadian Journal of Cardiology*. 21(2005):485
- Bogner. *American Journal of Managed Care*. 19(2013):e85
- Bolkan. *Psychiatric Services*. E-published 2/1/13
- Boswell. *American Journal of Pharmacy Benefits*. 4(2012):e97
- Bosworth. *International Journal of Geriatric Psychiatry*. 239(2008):129
- Bouhnik. *Antiviral Therapy*. 10(2005):53
- Bramley. *Journal of Managed Care Pharmacy*. 12(2006):239
- Broekmans. *International Journal of Nursing Studies*. 47(2010):1408
- Bryson. *Annals of Internal Medicine*. 149(2008):795
- Butler. *American Journal of Managed Care*. 17(2011):53
- Butt. *Liver International*. 30(2010):240
- Buvat. *Journal of Sex Medicine*. E-published 2/2/13
- Caetano. *Clinical Therapeutics*. 28(2006):1411
- Caisley. *European Psychiatry*. 27(2012):343
- Calip. *Breast Cancer Research and Treatment*. E-published 1/29/13

Campos-Rodriguez. *Annals of Internal Medicine*. 17(2012):115  
Carls. *Journal of Occupational and Environmental Medicine*. 54(2012):792  
Carney. *Health Psychology*. 14(1995):88  
Carpentier. *Epilepsia*. 54(2013):e20  
Caseiro. *Journal of Psychiatric Research*. 46(2012):1099  
Cecere. *COPD*. 9(2012):251  
Cervený. *Inflammatory Bowel Disease*. 13(2007):1244  
Chambers. *Rheumatology*. 48(2009):266  
Chan. *Medical Care*. 48(2011):196  
Chapman. *Drugs and Aging*. 25(2008):885  
Chapman and Benner. *Archives of Internal Medicine*. 165(2005):147  
Chen. *Journal of Managed Care Pharmacy*. 19(2013):291  
Chisholm-Burns. *Clinical Transplantation*. 26(2012):706  
Chotiyaputta. *Hepatology*. 52, Supplement(2010):542A  
Chotiyaputta and Hongthanakorn. *Journal of Viral Hepatitis*. 19(2012):205  
Claxton. *Clinical Therapeutics*. 23(2001):1296  
Cohen. *Journal of Clinical Psychiatry*. 73, Supplement 1(2012):31  
Coleman. *Journal of Managed Care Pharmacy*. 18(2012):527  
Colubi. *HIV Clinical Trials*. 13(2012):289  
Cooke. *Journal of Family Practice*. 60(2011):321  
Corrao. *Clinical Therapeutics*. 32(2010):300  
Corsonello. *Therapeutics and Clinical Risk Management*. 5(2009):209  
Coups. *Cancer Epidemiology, Biomarkers and Prevention*. 16(2007):510  
Cox. *Alcoholism Clinical and Experimental Research*. 20(1996):327  
Cramer. *Diabetes Care*. 27(2004):1218  
Cramer and Benedict. *International Journal of Clinical Practice*. 62(2008):76  
Cui. *Journal of Pain Research*. 5(2012):193  
Currie. *Diabetes Care*. 35(2012):1279  
Currie and Peyrot. *Journal of Diabetes Complications*. 27(2013):219  
Daley. *Parkinsonism and Related Disorders*. 18(2012):1053  
Davis. *Epilepsia*. 49(2008):446  
Davis and Edin. *Movement Disorders*. 25(2010):474  
Davis and Jandrisevits. *Journal of Emergency Medicine*. 43(2012):773  
Decker. *American Heart Journal*. 157(2009):556  
Degli Esposti. *Clinical Therapeutics*. 34(2012):190  
Dempe. *Journal of Psychosomatic Research*. 74(2013):122  
Demyttenaere. *Journal of Clinical Psychiatry*. 61, Supplement(2001):30  
Demyttenaere and Adelin. *International Journal of Psychopharmacology*. 23(2008):36  
De Smet. *Annals of Pharmacotherapy*. 40(2006):414  
Devaux. *Journal of the European Academy of Dermatology and Venereology*. 26, Supplement 3(2012):61  
Dezenti. *Journal of Clinical Oncology*. 28(2010):2423  
DiMatteo. *Medical Care*. 45(2007):521  
Dormuth. *Circulation*. 119(2009):2051

Egede. *Diabetes Care*. 35(2012):2533  
Elkout. *PLoS ONE*. 7(2012):e39130  
El-Serag. *American Journal of Gastroenterology*. 104(2009):2161  
Evans. *Journal of Managed Care Pharmacy*. 15(2009):476  
Fallis. *PLoS ONE*. 8(2013):e61735  
Ferguson. *Patient and Related Outcome Measures*. 2(2011):111  
Fischer. *Journal of General Internal Medicine*. 25(2010):284  
Fitzgerald. *Journal of Cardiac Failure*. 17(2011):664  
Fontein. *European Journal of Surgical Oncology*. 38(2012):110  
Foody. *Current Medical Research and Opinion*. 24(2008):1987  
Gadkari. *BMC Health Services Research*. 12(2012):98  
Gagnadoux. *PLoS ONE*. 6(2011):e22503  
Galetke. *Respiration*. 82(2011):155  
Gau. *Journal of Clinical Psychiatry*. 69(2008):131  
Gellad. *American Journal of Geriatric Pharmacology*. 9(2011):11  
Gentil. *Journal of the American Geriatric Society*. 60(2012):2297  
Glazer. *Journal of Cardiopulmonary Rehabilitation*. 22(2002):40  
Glombiewski. *PLoS ONE*. 7(2012):e50537  
Gohar. *BMC Complementary and Alternative Medicine*. 8(2008):4  
Gomes. *Archives of Internal Medicine*. 172(2012):1687[letter]  
Gonzalez. *Diabetes Care*. 30(2007):2222  
Gotay. *Expert Reviews in Pharmacoeconomics Outcome Research*. 11(2011):709  
Grant. *Diabetes Care*. 30(2007):807  
Grenard. *Journal of General Internal Medicine*. 26(2011):1175  
Guerin. *Current Medical Research and Opinion*. 28(2012):1155  
Ha. *Digestive Diseases and Sciences*. 56(2011):2423  
Halpern. *PM&R: The Journal of Injury, Function and Rehabilitation*. E-published 5/3/13  
Hartz. *Emerging Themes in Epidemiology*. 10(2013):1  
Hauber. *Diabetes Medicine*. 26(2009):416  
Hawkins. *Heart and Lung*. 41(2012):572  
Hayton. *Respiratory Medicine*. 107(2013):401  
Heisler. *Circulation*. 125(2012):2863  
Hershman. *Journal of Clinical Oncology*. 27(2010):4120  
Hertz. *Clinical Therapeutics*. 27(2005):1064  
Hillary. *American Journal of Managed Care*. 19(2013):e85  
Hlatky. *Journal of the American College of Cardiology*. 61(2013):295  
Ho. *American Journal of Medicine*. 155(2008):772  
Hohmann. *Stroke*. 44(2013):522  
Holt. *Journal of the American Geriatric Society*. 61(2013):558  
Holt and Muntner. *American Journal of Epidemiology*. 176, Supplement(2012):S64  
Hudson. *Journal of the American Board of Family Medicine*. 25(2012):782  
Iborra-Molto. *Nefrologia*. 32(2012):477  
Irvin. *Journal of Clinical Hypertension (Greenwich)*. 14(2012):694  
Irvine. *Psychosomatic Medicine*. 61(1999):566

Jackevicius. *Circulation*. 117(2008):1028  
Jackson. *American Journal of Gastroenterology*. 105(2010):525  
Julian. *Arthritis & Rheumatism*. 61(2009):240  
Kahn. *Medical Care*. 45(2007):431  
Kane. *CNS Spectrum*. 12, Supplement(2007):21  
Karter. *Medical Care*. 42(2004):110  
Kassab. *International Journal of Clinical Epidemiology*. E-published 1/3/13  
Kawakami. *Journal of Gastroenterology*. E-published 12/4/12  
Kennedy. *Journal of Managed Care Pharmacy*. 14(2008):553  
Khan. *Alimentary Pharmacology and Therapeutics*. 36(2012):755  
Khera. *Biology of Bone Marrow Transplantation*. 17(2011):995  
Khdour. *European Journal of Clinical Pharmacology*. 68(2012):1365  
Kiel. *Journal of Allergy and Immunology*. E-published 5/4/13  
Kindmalm. *Acta Diabetologica*. 44(2007):209  
Kivelevitch. *International Journal of Dermatology*. 51(2012):416  
Kohler. *Thorax*. 65(2010):829  
Koneru. *Journal of Clinical Rheumatology*. 14(2008):195  
Kongkaew. *Archives of Cardiovascular Disease*. 105(2012):507  
Kothawala. *Mayo Clinic Proceedings*. 82(2007):1493  
Krapek. *Annals of Pharmacotherapy*. 38(2004):1357  
Kronish. *Progress in Cardiovascular Disease*. 55(2013):S90  
Kronish and Edmundson. *Stroke*. 43(2012):2192  
Krousel-Wood. *Medical Clinics of North America*. 93(2009):753  
Krymchantowski. *MedGeneral Medicine*. 9(2007):21  
Kugler. *Journal of Nephrology*. 24(2011):366  
Laba. *BMC Family Practice*. 13(2012):61  
Lachaine. *American Heart Journal*. 152(2006):164  
Lagu. *American Journal of Managed Care*. 15(2009):24  
Lamba. *Clinical Transplantation*. 26(2012):328  
Lash. *British Cancer Research Journal*. 99(2006):215  
Lakatos. *Journal of Crohn's Disease and Colitis*. 4(2010):283  
Lawrence. *Journal of Managed Care Pharmacy*. 12(2006):466  
Lee. *PLoS ONE*. 8(2013):e62775  
Lehane. *Journal of Clinical Nursing*. 16(2007):1468  
Lemstra. *Canadian Journal of Cardiology*. 28(2012):574  
Lieber. *Digestive Diseases and Sciences*. 58(2013):824  
Lieveld. *Annals of Hepatology*. 12(2013):380  
Lim. *Psychiatric Investigation*. 9(2012):73  
Lin. *Cancer Prevention and Research (Philadelphia)*. 4(2011):1360  
Llor. *International Journal of Infectious Disease*. 10/29(2012):S1201  
Lu. *BMC Cancer*. 11(2011):279  
Lu and Roughead. *European Journal of Clinical Pharmacology*. 68(2012):65  
Lukin. *Journal of Cancer Education*. 27(2012):269  
Madbouly. *American Journal of Therapy*. E-published 3/8/12

Magai. *Journal of Women's Health*. 16(2007):11  
Makaryus. *Mayo Clinic Proceedings*. 80(2005):991  
Malla. *Psychological Medicine*. 38(2008):1585  
Malmenas. *Clinical Therapeutics*. E-published 5/1/13  
Mann. *Annals of Pharmacotherapy*. 44(2010):1410  
Mann and Glazer. *American Journal of Cardiology*. 111(2013):1437  
Mansur. *Drugs and Aging*. 25(2008):861  
Marcum. *Research in Social and Administrative Pharmacology*. E-published 1/3/13  
Marengo. *Lupus*. 21(2012):1158  
Margolis. *BMC Neurology*. 6(2011):122  
Marin. *Lancet*. 365(2005):1046  
Markkula. *Cancer Prevention and Research (Philadelphia)*. 5(2012):735  
Markotic. *Pain Medication*. E-published 1/31/13  
Marshall. *British Medical Journal*. 345(2012):14  
*American Heart Journal*. 165(2013):26  
Mazzaglia. *Circulation*. 120(2009):1598  
McCarthy. *Journal of the American Geriatric Society*. 48(2000):1226  
McHorney. *Health Expectations*. 14(2011):307  
Medic. *Neuropsychiatric Disease and Treatment*. 9(2013):119  
Melnikow. *Archives of Family Medicine*. 8(1999):510  
Menzin. *Journal of Managed Care Pharmacy*. 19, Supplement A (2013):S24  
Milano. *Critical Pathways in Cardiology*. 19(2011):35  
Mitra. *BMC Gastroenterology*. 12(2012):132  
Modi. *Journal of the American Medical Association*. 305(2011):1669  
Molinuevo. *Expert Reviews in Neurotherapeutics*. 12(2012):31  
Molloy. *Psychosomatic Medicine*. 74(2012):100  
Montes. *Patient Preference and Adherence*. 7(2013):89  
Mosley-Williams. *Arthritis & Rheumatism*. 47(2002):630  
Mumby. *Bone Marrow Transplantation*. 47(2012):556  
Murphy. *Thorax*. 67(2012):751  
Mulhem. *International Journal of Family Medicine*. 2013:ID901845  
Myong. *International Journal of Colorectal Disease*. 27(2012):1061  
Naderi. *American Journal of Medicine*. 125(2012):882  
Naderi and Barnett. *American Journal of Emergency Medicine*. 30(2012):347  
Nagrebetsky. *Diabetes Research and Clinical Practice*. 96(2012):119  
Nash. *Journal of Women's Health*. 16(2007):13  
Natarajan. *Canadian Family Physician*. 59(2013):e93  
Nekhlyudov. *Breast Cancer Research and Treatment*. 130(2011):681  
Neugaard. *Population Health Management*. 14(2011):99  
Neuget. *Journal of Clinical Oncology*. 19(2011):2534  
Newby. *Circulation*. 113(2009):203  
Nielsen. *Diabetology and Metabolic Syndrome*. 4(2012):23  
Obias-Manno. *Annals of Epidemiology*. 6(1996):93  
Odegard. *Diabetes Education*. 33(2007):1014

Oladapo. *Clinical Therapeutics*. 34(2012):605  
Olsen. *Osteoporosis International*. E-published 4/20/13  
Osterberg. *New England Journal of Medicine*. 353(2005):487  
Owusu. *Journal of Clinical Oncology*. 26(2008):549  
Padula. *American Journal of Medicine*. 125(2012):804  
Pampallona. *British Journal of Psychiatry*. 180(2012):104  
Partridge. *Journal of Clinical Oncology*. 21(2003):602  
Patrick. *Value in Healthcare*. 14(2011):513  
Pedan. *Journal of Managed Care Pharmacy*. 13(2007):487  
Perreault. *European Journal of Clinical Pharmacology*. 64(2008):1013  
Perreault and Lamarre. *Annals of Pharmacotherapy*. 39(2005):1401  
Pittman. *American Journal of Cardiology*. 110(2012):1459  
Pladevall. *Diabetes Care*. 27(2004):2800  
Pladewell. *American Journal of Epidemiology*. 165,Supplement(2007):S11  
Qian. *International Journal of Geriatric Psychiatry*. E-published 4/19/13  
Rabinowich. *Heart*. 98(2012):1817  
Rahman. *Ethnicity and Disease*. 13(2003):477  
Ram. *Current Hypertension Reports*. 8(2006):398  
Rank. *Journal of Allergy and Clinical Immunology*. 131(2013):724  
Raum. *Diabetes Research and Clinical Practice*. 97(2012):377  
Reach. *Diabetes Research and Clinical Practice*. 98(2012):19  
Reynolds. *Osteoporosis International*. E-published 4/18/13  
Restrepo. *International Journal of COPD*. 3(2008):371  
Rhee. *Diabetes Education*. 31(2005):240  
Richy. *Applied Health Economics and Policy*. E-published 5/7/13  
Rieckmann. *Journal of the American College of Cardiology*. 48(2006):2218  
Ridsdale. *British Journal of General Practice*. 61(2011):e271  
Riis. *Scandinavian Journal of Gastroenterology*. 47(2012):649  
Robinson. *Journal of the American College of Cardiology*. 51,Supplement A(2008):A363  
Robinson and Long. *Journal of Managed Care Pharmacy*. 12(2006):43  
Rojas. *Journal of Lower Genitourinary Tract Disease*. E-published 5/2/13  
Rolnick. *Clinical Medical Research*. E-published 4/12/13  
Rothenbacher. *BMC Family Practice*. 7(2006):42  
Roughead. *European Journal of Cardiology Prevention and Rehabilitation*. 17(2010):71  
Roumie. *Annals of Internal Medicine*. 156(2012):834[editorial]  
Rudnicki. *Health Progress*. 88(2007):62  
Rushworth. *International Journal of Pharmacy Practice*. 29(2012):226  
Ryder. *Southern Medical Journal*. 105(2012):325  
Sabit. *Respiratory Medicine*. 102(2008):819  
Saini. *American Journal of Managed Care*. 15(2009):e22  
Sajatovic. *Comprehensive Psychiatry*. 52(2011):280  
Sanchez. *Sleep Medicine Reviews*. 13(2009):223  
Sanfelix-Gimeno. *Journal of Managed Care Pharmacy*. 19(2013):247  
Santana. *Journal of Psychiatric Practice*. 19(2013):42

Schectman. *Journal of General Internal Medicine*. 23(2008):1665  
Schoenthaler. *Diabetes Education*. 38(2012):397  
Schueler. *Journal of Women's Health*. 17(2008):1477  
Schulman. *Journal of Thrombosis and Hemostasis*. E-published 4/13/13  
Senst. *American Journal of Health Systems Pharmacy*. 58(2001):1126  
Serna. *European Psychiatry*. 25(2010):206  
Sexton. *International Journal of Clinical Practice*. 65(2011):567  
Shah. *Clinical Geriatric Medicine*. 28(2012):173  
Shah and Hirsch. *Journal of General Internal Medicine*. 24(2009):233  
Sharp. *Cytopathology*. 23(2012):150  
Sheehan. *CNS Drugs*. 22(2008):963  
Shin. *American Journal of Managed Care*. 18(2012):426  
Simon. *General Hospital Psychiatry*. E-published 11/8/12  
Simoni-Wastila. *American Journal of Geriatric Psychopharmacology*. 10(2012):201  
Simpson. *British Medical Journal*. 333(2006):15  
Smith. *Annals of Pharmacotherapy*. 41(2007):116  
Sockalingam. *Journal of Hepatology*. 57(2012):1299  
Sofianou. *Journal of General Internal Medicine*. 28(2013):67  
Sokol. *Medical Care*. 43(2005):521  
Song. *Journal of Cardiovascular Nursing*. 24(2009):299  
Steinberg. *Clinical Drug Investigations*. 30(2010):89  
Stilley. *Progress in Transplantation*. 20(2010):58  
Stoehr. *American Journal of Managed Care*. 6(2008):255  
Suzuki. *Journal of the American Geriatric Society*. 58(2010):1007[letter]  
Swimberghe. *Annals of Dermatology*. 25(2013):28  
Swindle. *American Journal of Geriatric Pharmacotherapy*. 9(2011):471  
Tang. *Clinical Nursing Research*. E-published 4/2/13  
Thiruchselvan. *International Journal of Geriatric Psychiatry*. 27(2012):1275  
Ting. *Journal of Rheumatology*. 39(2012):174  
Tiv. *PLoS ONE*. 7(2012):e32412  
Tsai. *Journal of Glaucoma*. 12(2003):393  
Valdya. *Patient Preference and Adherence*. 7(2013):21  
Valeberg. *Clinical Journal of Pain*. 24(2008):627  
van Servellen. *Mental Health in Family Medicine*. 8(2011):255  
Vik. *Drugs and Aging*. 23(2006):345  
Virdi. *Diabetes Technology and Therapy*. 14(2012):790  
Vyas. *Journal of Community Health*. 37(2012):632  
Wang. *Journal of General Internal Medicine*. 17(2002):504  
Wang and Liu. *Current Medical Research and Opinion*. 27(2011):1303  
Ward. *Osteoporosis International*. E-published 10/26/12  
Weizman. *Alimentary Pharmacology and Therapeutics*. 35(2012):342  
Wessels. *International Journal of Psychopharmacology*. 27(2012):291  
Wigertz. *Breast Cancer Research and Treatment*. 133(2012):367  
Willemen. *Drug Safety*. 35(2012):1147

Williams. *Psychology and Health*. 26(2011):703  
Whooley. *Journal of the American Medical Association*. 300(2008):2379  
Wong. *International Journal of Cardiology*. 11/19/12:S0167  
Wray. *Pediatric Transplantation*. 10(2006):694  
Wroth. *Journal of the American Board of Family Health*. 19(2006):478  
Wu. *Annals of Pharmacotherapy*. 45(2011):342  
Wu and Zhu. *Breast Cancer Research and Treatment*. 101(2007):317  
Wutoh. *Journal of the International Medical Association*. 93(2001):243  
Yang. *Clinical Therapy*. 31(2009):2178  
Yen. *American Journal of Pharmacy Benefits*. 5(2013):e15  
Zhang. *American Heart Journal*. 164(2012):425  
Zhao. *Current Medical Research and Opinion*. 27(2011):785  
Zeber. *Canadian Family Physician*. 56(2010):e302  
Ziller. *International Journal of Clinical Pharmacology and Therapeutics*. 50(2012):315