Compliance and Persistence with Osteoporosis Therapies

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The US Food and Drug Administration has approved a diverse group of effective osteoporosis therapies. However, these therapies obviously only work when patients with osteoporosis take them. Data from retrospective observational databases have shown poor compliance and persistence with all osteoporosis drugs, particularly oral bisphosphonate therapy. Patients on weekly therapies are more compliant and persistent than those on daily dosing. Data have also shown decreased fracture risk, decreased health care utilization, and lower costs in compliant and persistent patients.

Introduction

In chronic diseases such as osteoporosis, poor compliance and persistence with medication are common. The World Health Organization recently stated that noncompliance and nonpersistence in the treatment of chronic diseases are worldwide problems of striking magnitude—in developed countries and developing countries, patients average just 50% compliance and persistence [1]. Poor patient compliance is compounded by the fact that until a fracture occurs, osteoporosis is asymptomatic. Poor follow-up regarding medication compliance for osteoporosis has been associated with increased health care utilization, clinical consequences, and exorbitant cost.

This review focuses on patient behaviors in taking osteoporosis therapies, particularly oral bisphosphonates, as well as on the consequences of poor compliance and persistence with these therapies.

Definitions

This review uses definitions from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) for persistence and compliance [2••]. Persistence is defined as the "accumulation of time from initiation to discontinuation of therapy," meaning the length of treatment without a gap in refills (gap length is variable across studies). Compliance, defined as "the extent to which a patient acts in accordance with the prescribed interval and dose as well as dosing regimen," is measured by calculating the medication possession ratio (MPR) (ie, the number of days' supply of medication received divided by the length of the follow-up period). ISPOR defines adherence as a potentially less pejorative synonym for compliance but discourages its use because of potential confusion. Others have defined adherence as a term to encompass both compliance and persistence, but because there is no standard for measurement of these combined phenomena, this definition is somewhat less useful.

Weekly and Daily Bisphosphonate Therapy

Currently, bisphosphonates are the gold standard for treatment of postmenopausal osteoporosis with established vertebral, nonvertebral, and hip fracture efficacy. The US Food and Drug Administration has approved four bisphosphonates: alendronate, ibandronate, risedronate, and zoledronic acid. Oral bisphosphonates are available for dosing daily (alendronate, risedronate), weekly (alendronate, risedronate), or monthly (ibandronate once a month, risedronate 2 consecutive days per month). Bisphosphonates are also available yearly as intravenous (IV) zoledronic acid or every 3 months as IV ibandronate.

Administrative claims data are available for the oral formulations that have been on the market for several years. Six retrospective databases offer comparisons between daily and weekly bisphosphonates for persistence and compliance [3–8]. The mean MPR was consistently higher for weekly therapy (0.58–0.76) versus daily therapy (0.46–0.64). Patients receiving weekly bisphosphonates exhibited better persistence (length of persistence 194–269 days; 35.7%–69.7% persistent) compared with those receiving daily therapy (length of persistence 134–208 days; 26.1%–55.7% persistent). All the studies that examined compliance and persistence in patients receiving daily and weekly bisphosphonates found the same pattern—

Table 1. One-year persistence and compliance data for daily and weekly bisphosphonates

Study	Daily				Weekly			
	n	Mean MPR	Persistence, *days*	Persistent, %	*n*	Mean MPR	Persistence, *days*	Persistent, %
Recker et al. [3], Sunyecz et al. [4], Ettinger et al. [5]	33,767	0.54	198	39	177,552	0.65	238	56.7
Cramer et al. [6]	2010	0.58	134	31.7	731	0.69	269	44.2
Gold et al. [24]	2784	0.52	177	26.1	1985	0.58	194	35.7
Brankin et al. [7]								
GPRD	1104	0.64	208	39.5	6463	0.76	249	51.9
MEDIPLUS	860	0.56	186	33.3	5102	0.7	228	43.6
DIN	67	0.46	189	55.7	1734	0.6	235	69.7
Cramer et al. [8]	1363	0.53	155	44	3969	0.59	179	51

DIN—Doctors' Independent Network database; GPRD—General Practice Research Database; MEDIPLUS—IMS Disease Analyzer (IMS Health, London); MPR—medication possession ratio.
(*From* Cramer et al. [25], with permission.)

patients exhibited better medication-taking behavior with weekly therapy.

These studies showed considerable variability in compliance measured as MPR or persistence. For example, persistence rates ranged from 17.9% to 78% for a weekly bisphosphonate (Table 1). Possible explanations include differences in definitions and measurement of compliance and persistence, methodology, and sample demographics. One important and seemingly recurring problem is related to authors' definitions of nonpersistence with therapy. The gap between refills when a patient is not persistent is called the refill gap.

Compliance data for weekly bisphosphonates fall within a much smaller range, with mean MPR values of 0.59 to 0.81. Compliance data comparisons are confounded by the varying follow-up periods used in the studies. MPR calculation depends on the length of the follow-up period. This variation must be considered when evaluating studies with different time frames.

Persistence with Weekly Versus Monthly Bisphosphonates

Silverman et al. [9] evaluated medication persistence among patients receiving monthly ibandronate versus weekly bisphosphonates using 12-month results of two large managed care claims databases. Women who were prescribed monthly ibandronate were more persistent than women on weekly bisphosphonates; at 12 months, persistence was 36% on monthly therapy in both databases and was 25% and 27% on weekly therapy. The Persistence Study of Ibandronate versus Alendronate (PERSIST) compared persistence with monthly ibandronate with a patient support program to weekly bisphosphonate therapy. Compared with alendronate, researchers found a 47% improvement in the proportion of patients persisting on ibandronate [10].

However, two recent studies using pharmacy claims databases did not find improved persistence with monthly drugs. Gold et al. [11] found significantly higher mean persistence for weekly risedronate than for monthly ibandronate patients (144 vs 100 days, $P < 0.0001$) in a 6-month study. Weiss et al. [12] analyzed 12-month retail prescription data from 165,000 women ages 50 years and older who were new to osteoporosis therapy. They found better persistence with weekly alendronate (116 days) and risedronate (113 days) than with monthly ibandronate (98 days) ($P < 0.0001$). However, pharmacy databases cannot fully correct for channeling or selection bias, which may occur when physicians choose a medication. For example, using two administrative claims databases, Silverman et al. [9] found greater prevalence of rheumatoid arthritis and gastrointestinal disease in patients taking ibandronate. These pharmacy database studies also did not include sensitivity analyses across multiple refill gaps.

Database Limitations

Information from patient databases has numerous advantages and certain inherent limitations [13•,14,15]. Data are obtained from patients in an unrestricted "real world" clinical setting, in contrast to data from structured clinical trials, which could be biased because of the randomized clinical trial atmosphere. Administrative databases also allow access to a large sample size of patients, which can far exceed the number of patients included in clinical trials. Depending on physician perception of different medications, though, patients may be channeled to certain medications, which may have significant impact on discontinuation rates [15]. Because claims data are collected primarily for administrative purposes, billing and coding errors may occur, which can inflate or deflate the calculation of persistence and

compliance. In addition, claims data do not account for medication samples that may be given at physician's offices, which can influence refill patterns and might make a patient seem nonpersistent or noncompliant. Patients who change providers, health plans, or osteoporosis medications may also be seen as nonpersistent. In addition, patients who suffer a fracture might receive their medication in a hospital or rehab setting, which may not be captured in the database [14]. However, few alternatives to these databases exist when a research question calls for longitudinal data for a large group over a specific amount of time.

Consequences of Poor Compliance and Persistence with Osteoporosis Therapies

Poor persistence with bisphosphonates can lead to smaller decreases in bone turnover and smaller improvements in bone mineral density [16,17•]. Siris et al. [18••] found that women who complied up to 50% of the time with their medication as measured by MPR showed only minimal fracture reduction from their oral bisphosphonates, whereas those who complied 80% or more of the time showed a significant reduction in fracture rates. In a study of claims data, Caro et al. [19] found that patients who complied with their osteoporosis therapy showed a significantly reduced fracture rate (16%) when compared with their noncompliant peers. Weycker et al. [20] found that those who were compliant 90% or more of the time showed significantly reduced fracture risk (OR = 0.70, 95% CI, 0.52–0.93) than did those with an MPR less than 30. In the long term, poor compliance will lead to increased health care costs, because adverse events such as fractures are more likely [21,22]. McCombs et al. [23] has shown that a decrease in fracture rates leads to reduced physician services, hospitalization services, and outpatient care, all of which lead to reduced health care costs. Gold et al. [24] has also shown that poor persistence with therapy resulted in a 26% increased risk of fractures.

Reasons for Inadequate Compliance and Persistence

We have only begun to understand why patients do not take their medication. Some factors that reduce compliance include high costs of medication, complicated dosing regimens, fear of side effects, concern about drug interactions, lack of understanding about osteoporosis, use of multiple medications, and poor patient-provider communication [25]. Also, some patients simply forget. Whatever the reasons, abysmal compliance and persistence are a cause for future concern. As the American population ages, the number of people with osteoporosis will increase, making it even more important that people comply with therapeutic recommendations to avoid fractures.

Lessons from Other Rheumatic Diseases

Poor compliance and persistence with therapies is a problem in all rheumatic diseases [26,27]. Studies of these behaviors in osteoarthritis have identified racial differences in taking analgesic/anti-inflammatory medications [27]. Nived et al. [28] found that education level was the best predictor of compliance with medication prescriptions. In a study of compliance and persistence in rheumatoid arthritis, polymyalgia rheumatica, and gout, de Klerk et al. [26] used multiple regression analyses to find that the social and biologic factors of class of medication (symptom relieving, disease controlling), dosing frequency, gender, coping pattern, and overall health explained 67% of the variance in medication compliance.

How We Can Improve Compliance and Persistence

Rheumatologists must educate patients about the importance of compliance and persistence and how best to achieve them. Educational programs combined with reminder systems (eg, e-mail reminders, phone contacts) facilitated by allied health care professionals in physicians' offices can have a positive impact on patient behaviors. For example, a study of medication compliance showed that nurse monitoring of patients with osteoporosis increased compliance with raloxifene by 57% when compared with the no-reminder group [29]. In administrative databases, some evidence suggests that extended prescriptions (eg, 90 days vs 30 days) could improve persistence.

As suggested by Lewiecki [30], physicians can do four things to help improve compliance and persistence: be better listeners, be better communicators, participate in shared decision making, and reinforce patient compliance and persistence by monitoring response to therapy and addressing fears of side effects.

Our patients may be unconvinced that they have osteoporosis: they have taken calcium, they exercise regularly, and they have no symptoms. In addition, they may be unconvinced of the consequences of osteoporosis and the need for treatment, because they often believe it is part of the normal aging process. Even after recognition that they have osteoporosis, they still may not be convinced of medication efficacy, or they may have fear of side effects. Once we explain to patients the positive risk benefit of taking their medication, other significant barriers such as cost or lifestyle change may prevent them from taking the medication. We can individualize the dosing frequency to our patients' preferences and lifestyles. Some patients who prefer a regular routine may prefer daily or weekly doses, whereas patients who have difficulty remembering to take their medication may prefer monthly or IV every three months or yearly doses.

Conclusions

Regardless of the therapy type, compliance and persistence with osteoporosis medications are poor. Compliance and persistence are better—though still suboptimal—in patients receiving weekly bisphosphonates compared with those receiving daily therapy. However, if we expect to make progress in our fight against osteoporosis, both compliance and persistence must be improved.

Disclosures

Dr. Silverman has worked on the Speaker's Bureau for Eli Lilly (Indianapolis, IN), Merck & Co. Inc. (Whitehouse Station, NJ), Procter & Gamble (Cincinnati, OH), and F. Hoffmann-La Roche Ltd. (Basel, Switzerland). He has worked as a consultant for Merck, Procter & Gamble, Wyeth (Madison, NJ), Roche, and Novartis International AG (Basel, Switzerland). Dr. Silverman has received research support from Novartis, Eli Lilly, Wyeth, Roche, Procter & Gamble, and Merck, and he has served on the Board of Directors for CompuMed Inc. (Los Angeles, CA).

Dr. Gold has worked as a consultant and speaker for Amgen (Thousand Oaks, CA), Procter & Gamble, GlaxoSmithKline (Raleigh, NC), F. Hoffman-La Roche Ltd., Sanofi-Aventis (Bridgewater, NJ), and Eli Lilly and has served on consultant boards for Procter & Gamble, Sanofi-Aventis, GlaxoSmithKline, Eli Lilly, and F. Hoffman-La Roche.

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