

The Diffusion of a Novel Therapy Into Clinical Practice

The Case of Sildenafil

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Background: Erectile dysfunction is a common condition, yet in the past most affected men did not seek medical treatment.

Objective: To examine how sildenafil (Viagra), a new medication for the treatment of erectile dysfunction, has been incorporated into general medical practice.

Subjects and Methods: The study population consisted of all male members of a group-model Massachusetts health maintenance organization (HMO) whose first prescription for sildenafil was dispensed during the first 24 weeks of its availability through the HMO as a plan benefit (April 24, 1998, through October 8, 1998). Data collected on each member in the study population included age, specialty of the prescribing physician, initial dose, use of prior treatments for erectile dysfunction, receipt of medications known to predispose to impotence, filling of a second prescription for sildenafil, and concomitant medical conditions (including hypertension, ischemic heart disease, hyperlipidemia, diabetes mellitus, and history of radical prostatectomy). Cross tabulations and logistic regression models were constructed to evaluate the potential associations between filling a second prescription for sildenafil and other characteristics of sildenafil users.

Results: We identified 899 members who filled a first-time sildenafil prescription in the 24-week period of interest. The majority of sildenafil prescriptions that were

filled for the first time (85%) occurred in the first 12 weeks of its availability. Most sildenafil users (84%) were between 45 and 74 years of age (average age, 61 years; age range, 23 to 90 years), and approximately 40% had documentation of prior treatment for erectile dysfunction. Use was highest among those aged 55 to 64 years, with almost 5% of all male HMO members in that age group having received at least 1 sildenafil prescription. Our cohort of sildenafil users was significantly more likely to have hypertension ($P < .01$), hyperlipidemia ($P < .01$), and diabetes mellitus ($P < .01$) than persons who participated in a widely publicized clinical trial of the medication. Prescribing physicians were predominantly primary care physicians (78% were internists, and 11% were family practitioners). More than 60% of sildenafil users filled a second prescription within 3 months of the first prescription; in multivariate analyses, factors associated with filling a second prescription included younger age and prior treatment for erectile dysfunction.

Conclusions: Sildenafil was rapidly adopted into the clinical practice of primary care physicians for the treatment of erectile dysfunction in the managed care setting. The patients for whom the drug was prescribed in the general practice setting differed across many medical characteristics from study subjects who participated in clinical trials of the drug.

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ERECTILE DYSFUNCTION is a common condition that is thought to affect between 20 and 30 million men in the United States,¹ the majority of whom have never sought medical attention for the problem.² With the availability of sildenafil (Viagra), there has been unprecedented public interest in the treatment of this condition.³ In the first 3 months that sildenafil was on the market, 3.9 million prescriptions were dispensed.⁴ The medication is even available for purchase over the Internet.^{5,6} The

introduction of an effective oral medication has shifted the treatment of erectile dysfunction from specialists to primary care physicians.⁷ Most specialists in male impotence consider sildenafil the first-line therapy for erectile dysfunction.⁷

Little is known regarding how new medications are incorporated into clinical practice. Physician characteristics and economic considerations clearly influence the adoption of new therapies.⁸ The greater media attention given to medical therapeutic advances and the recent changes in policies and practices regard-

SUBJECTS AND METHODS

STUDY SETTING

The Fallon Community Health Plan is a mixed-model HMO that has been operating in the central and eastern areas of Massachusetts since 1977. The group-model component is composed of a large multispecialty group practice with more than 200 physicians providing care to approximately 150,000 members. More than 90% of the health plan members are covered by a drug benefit plan, with a nominal copayment for each prescription. For those members who make out-of-pocket purchases of drugs, prescriptions are favorably priced at or near the average wholesale price for the agent.

The computerized information system of the health plan contains records on the use of all health care services and prescriptions filled, collected as part of routine fiscal activities, as well as the results of laboratory studies. Each prescription record contains a unique patient identification number as well as the medication name, date the prescription was filled, number of tablets dispensed, and dose per tablet.

STUDY POPULATION

The study population comprised all members of the health plan in the group-model component who enrolled between April 1, 1998, and January 31, 1999, and who filled a prescription for sildenafil in the first 24 weeks of its availability as a plan benefit (April 24, 1998, through October 8, 1998).

First-time prescriptions for sildenafil required completion by the prescribing physician of a special order form

that included information on the age of the patient, indication for the treatment, and prior treatments that had been used for erectile dysfunction. This information was not used to qualify patients for, or to disqualify patients from, treatment. Before filling a sildenafil prescription, the pharmacist reviewed the patient's medical history and current medication profile to reduce the risk of drug or disease interactions. If the pharmacist had any concerns, the primary care physician was contacted. Sildenafil was not dispensed if the patient was concurrently taking nitrates. The evaluation of erectile dysfunction before treatment with sildenafil was determined solely by the prescribing physician. Information was not ascertained on the effectiveness of sildenafil or on the reasons for discontinuation of the treatment.

Automated administrative databases were used to obtain information on all drug dispensings of sildenafil including dose, concomitant prescribed drug therapies, medical diagnoses, and selected laboratory results. The number of tablets dispensed per prescription generally did not exceed 4.

PATIENT AND PRESCRIBER CHARACTERISTICS

Sildenafil users were characterized according to age group (<45, 45-54, 55-64, 65-74, or ≥75 years) and initial dose of sildenafil (25, 50, or 100 mg), as recorded on the special order form for sildenafil that was filled out by the prescribing physician. A medical chart abstraction using computerized provider notes was performed. The most recent comprehensive history and physical examination results obtained within the 1-year period, as well as all available notes from physician visits in the 3-month period before the first sildenafil prescription was dispensed, were reviewed for relevant clinical information. Selected diagnoses of interest

ing direct marketing to patients have allowed consumers to have a greater role in the process of therapeutic decision making. The case of sildenafil provides a unique opportunity to study the diffusion of a novel, widely advertised, and desired therapy into the general medical practice setting.

The purpose of our study was to examine the use of sildenafil in the first 6 months of its availability in a managed care setting to determine prescribing trends, characteristics of sildenafil users, prescriber characteristics, and usage patterns in a cohort of sildenafil users.

RESULTS

We identified 899 HMO members who filled first-time sildenafil prescriptions in the initial 24 weeks of its availability as a benefit through the health plan. They were all men between 23 and 90 years of age (mean [SD] age, 61 [10.4] years). The majority of patients (85%) were between 45 and 74 years of age (**Table 1**). More than 50% of the patients received 50 mg as the initial dose of sildenafil. Almost 60% of the patients had no documentation of prior treatment for erectile dysfunction. Concomitant conditions, such as hypertension, ischemic heart disease, hyperlipidemia, and diabetes

mellitus, were common (**Table 1**). One third of patients had filled prescriptions for medications known to predispose to impotence in the calendar year before they received sildenafil.

The prevalence of sildenafil use among HMO members varied according to age. Use was highest among those aged 55 to 64 years, with almost 5% of male HMO members in that age group having received at least 1 prescription for sildenafil (**Table 2**). Internists prescribed the medication for most patients (78%); family practitioners and urologists prescribed the medication for 11% and 8% of the patients, respectively. During the 24-week study, the number of sildenafil prescriptions that were filled for the first time declined (**Figure**). More than 80% of the first-time sildenafil prescriptions that were filled in this 24-week period occurred in the first 12 weeks of its availability.

A "second fill" was defined as a second prescription that was filled within 3 months of the first prescription. There were 545 members (61%) who filled at least 1 additional prescription during this period. Those who filled a second prescription were compared with those who did not (**Table 3**). Across the relevant age groups (ie, <45, 45-54, 55-64, 65-74 and ≥75 years), 75%, 62%, 62%, 57%, and 56%, respectively, filled a second prescription (test for trend, $P = .01$). In univariate analyses,

included hypertension, ischemic heart disease, hyperlipidemia, diabetes mellitus, and history of radical prostatectomy. If none of these selected conditions was discussed in the available provider notes, dispensed medications were used as surrogate markers of the conditions.

All patients without a diagnosis of hypertension who were receiving selected antihypertensive agents (eg, β -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, central α_2 -agonists, thiazide diuretics, peripheral vasodilators, or sympatholytic agents) were identified, and information contained in provider notes was reviewed. If there was no mention of a condition for which the antihypertensive agent was prescribed, the patient was characterized as having hypertension. A patient who had received nitrates in the past was characterized as having ischemic heart disease (all patients who had received nitrate therapy were informed that they could not concurrently take sildenafil and nitrates). A patient was considered to have hyperlipidemia if a lipid-lowering agent had been prescribed for him or if he had had a total serum cholesterol level of 6.22 mmol/L (240 mg/dL) or higher within the 2-year period before he received sildenafil.⁹ A patient was considered to have diabetes mellitus if a hypoglycemic agent had been prescribed for him or if he had had a serum glucose level of 11.1 mmol/L (200 mg/dL) or higher within the 2-year period before he received sildenafil.

Prior treatment for erectile dysfunction included the use of vacuum erection devices, yohimbine hydrochloride, testosterone cypionate, testosterone enanthate, penile injections of alprostadil, intraurethral suppositories of alprostadil, penile injections of papaverine, penile implants, annular rings, or dehydroepiandrosterone. Patients were also characterized in regard to their use of selected medications that can predispose to impotence (eg,

thiazide diuretics, spironolactone, sympatholytic agents, β -blockers, antipsychotic agents, monoamine oxidase inhibitors, fluoxetine, lithium carbonate, lithium citrate, digoxin, clofibrate, and cimetidine hydrochloride^{10,11}). Prescribing physicians were divided into 4 specialty groups: family practice, internal medicine, urology, and other.

STATISTICAL ANALYSIS

Using automated pharmacy data, prescribing trends were assessed. The number of first-time sildenafil dispensings was assessed for each 4-week period during the 24-week study period. The prevalence of sildenafil dispensings among HMO members was calculated for 5 age groups (<45, 45-54, 55-64, 65-74, and ≥ 75 years), with the denominator including all male enrollees within each respective age group. The reference group consisted of subjects aged 55 to 64 years.

To assess comparability with study subjects participating in a premarketing study that was widely publicized,¹² selected characteristics of our study sample were compared with those of subjects who received sildenafil in the clinical trial setting using the χ^2 test. The characteristics of interest included patient age and selected conditions, including hypertension, ischemic heart disease, hyperlipidemia, diabetes mellitus, and history of radical prostatectomy.

We identified sildenafil users who filled a second prescription during the 3-month period after the initial prescription. Cross tabulations and logistic regression models were constructed to evaluate the potential associations between the filling of a second prescription and patient age, prior treatment for erectile dysfunction, diagnosis of ischemic heart disease, and receipt of medications known to predispose to impotence.

sildenafil users who had received prior treatment for erectile dysfunction were slightly more likely to fill a second prescription (relative risk [RR] 1.14; 95% confidence interval [CI], 1.03-1.26). Also, sildenafil users who had a diagnosis of ischemic heart disease (RR, 0.85; 95% CI, 0.73-1.00) or who had received a medication associated with impotence (RR, 0.88; 95% CI, 0.78-0.99) were less likely to fill a second sildenafil prescription. Logistic regression modeling indicated that patient age and prior treatment for erectile dysfunction were independently associated with the filling of a second prescription for sildenafil. Patients younger than 45 years were significantly more likely to fill a second prescription than the subjects in the reference group (age range, 55-64 years) (odds ratio [OR], 1.86; 95% CI, 1.02-3.54). There were no significant differences between the other age groups and the reference group (45-54 years vs 55-64 years, $P = .99$; 65-74 years vs 55-64 years, $P = .31$; and ≥ 75 years, $P = .51$). Patients who had prior treatment for erectile dysfunction were more likely to fill a second prescription (OR, 1.43; 95% CI, 1.09-1.90).

The characteristics of sildenafil users differed substantially from those of the subjects who participated in a widely publicized clinical trial.¹² The members of the HMO cohort were significantly more likely to have hypertension ($P < .01$), hyperlipidemia ($P < .01$), or diabe-

tes mellitus than those who participated in the dose escalation study by Goldstein et al¹² ($P < .01$) (**Table 4**). However, the age characteristics of the study populations were similar.

COMMENT

We found that sildenafil was rapidly incorporated into the general practice setting over the 24-week period, with 85% of first-time prescriptions being filled in the first 12 weeks of its availability. Most sildenafil users (84%) were aged 45 to 74 years. Almost all sildenafil users (91%) had received their prescriptions from their primary care physicians. Approximately 60% of first-time sildenafil users filled a second prescription within 3 months of the first prescription.

Multiple factors influence the adoption of a new medication into medical practice. Characteristics of the medication itself affect use. Medications that are easy to administer and have a low perceived risk are used more readily. In situations in which the medical problem has been previously difficult to treat or has a poor prognosis, medications are adopted relatively rapidly.¹³ Information from pharmaceutical sales representatives^{13,14} and the media,¹⁵⁻¹⁷ directed both at health care providers and the public, has been shown to affect the use of medica-

Table 1. Patient Characteristics

Characteristics	Total Study Population, No. (%) (N = 899)
Age categories, y	
<45	63 (7)
45-54	177 (20)
55-64	298 (33)
65-74	284 (32)
≥75	77 (9)
Initial dose prescribed, mg	
25	311 (35)
50	529 (59)
100	59 (7)
Prior treatment for erectile dysfunction*	369 (41)
Yohimbine	199 (22)
Alprostadil injections	101 (11)
Vacuum erection devices	59 (7)
Alprostadil suppositories	48 (5)
Concomitant conditions	
Hypertension	443 (49)
Ischemic heart disease	147 (16)
Hyperlipidemia	376 (42)
History of radical prostatectomy	41 (5)
Diabetes mellitus	221 (25)
Receiving any medication associated with erectile dysfunction†	298 (33)

*Prior treatment also includes testosterone, penile injections of papaverine, penile implants, annular rings, and dehydroepiandrosterone.

†β-Blockers, thiazide diuretics, cimetidine, digoxin, fluoxetine, spironolactone, sympatholytic agents, antipsychotic agents, monoamine oxidase inhibitors, lithium, clofibrate, and cimetidine.

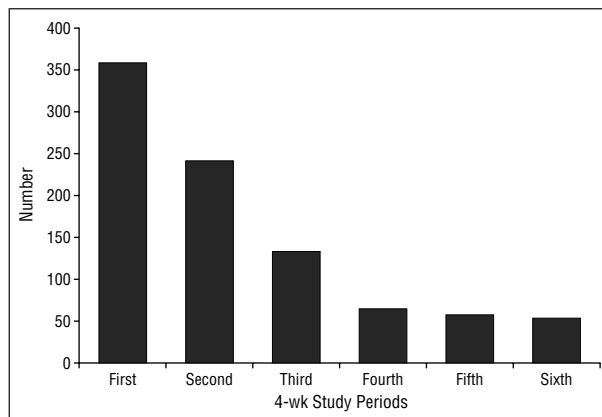
Table 2. Age Distribution of First-Time Sildenafil (Viagra) Users and Prevalence of Use Among HMO* Members by Age Group

Age Group, y	No. of First-Time Sildenafil Users	No. of HMO Members	Prevalence of Use, %
18-44	63	26 038	0.2
45-54	177	10 252	1.7
55-64	298	6398	4.7
65-74	284	6890	4.1
≥75	77	5456	1.4
Total	899	55 034	1.6

*HMO indicates health maintenance organization.

tions. Also, perceived patient demand by health care providers influences prescribing patterns.^{18,19} In the case of sildenafil, media attention has clearly resulted in a greater awareness of erectile dysfunction as a treatable condition and increased the demand for the drug.

Erectile dysfunction is a common condition that affects a considerable number of middle-aged to elderly men and is associated with diminished quality of life.²⁰ Data from the Massachusetts Male Aging Study indicated that 34.8% of males aged 40 to 70 years had moderate or complete erectile dysfunction.¹ Similarly, Laumann et al²¹ found that 11% of men aged 40 to 49 years and 18% of men aged 50 to 59 years had erectile dysfunction. While the prevalence of sildenafil use in our general practice setting approached 5% for some age groups, the overall



The number of first-time sildenafil (Viagra) prescriptions filled during sequential study periods.

Table 3. A Comparison of Sildenafil (Viagra) Users Who Filled a Second Prescription Within 3 Months of the First Prescription ("Second Fill") With Those Who Did Not ("No Second Fill")

Characteristics	Second Fill, No. (%) (n = 545)	No Second Fill, No. (%) (n = 354)
Age, y		
Mean	60	62
Range	23-89	32-90
Age categories, y*		
<45	47 (9)	16 (5)
45-54	110 (20)	67 (19)
55-64	184 (34)	114 (32)
65-74	161 (30)	123 (35)
≥75	43 (8)	34 (10)
Initial dose prescribed, mg		
25	198 (36)	113 (32)
50	313 (57)	217 (61)
100	34 (6)	25 (7)
Prior treatment for erectile dysfunction†‡	241 (44)	128 (36)
Concomitant conditions		
Hypertension	259 (48)	184 (52)
Ischemic heart disease†	78 (14)	69 (19)
Hyperlipidemia	215 (39)	161 (46)
History of radical prostatectomy	23 (4.2)	18 (5)
Diabetes mellitus	135 (25)	86 (24)
Receiving medications associated with erectile dysfunction†§	165 (30)	133 (38)

*P = .01, test for trend comparing age categories.

†P < .05.

‡Yohimbine, penile injections of alprostadil, vacuum erection devices, intraurethral suppositories of alprostadil, testosterone, penile injections of papaverine, penile implants, annular rings, and dehydroepiandrosterone.

§β-Blockers, thiazide diuretics, cimetidine, digoxin, fluoxetine, spironolactone, sympatholytic agents, antipsychotic agents, monoamine oxidase inhibitors, lithium, clofibrate, and cimetidine.

prevalence of erectile dysfunction in this population was likely to be substantially higher.

More than 60% of study subjects filled a second prescription within 3 months of filling the initial prescription. This was a substantially lower percentage than in the clinical trial setting, in which the persistence of medication use ranged between 85% and 94% over 12 to 32 weeks of observation.¹² In the general practice setting, discon-

Table 4. Characteristics of Our Patient Population and the Participants in the Clinical Trial¹²

Characteristic	Study Population	Clinical Trial Population
Mean age, y	61	60
Concomitant condition, %		
Hypertension*	49	24
Ischemic heart disease	16	15
Hyperlipidemia*	42	15
History of radical prostatectomy	5	9
Diabetes mellitus*	25	8

*P<.01.

Continuation of medications has been shown to be greater than has been demonstrated in randomized clinical trials.²² For example, in the New Jersey Medicaid population, Gurwitz et al²³ determined that only 77% of elderly patients with glaucoma filled a second prescription for glaucoma treatment over a 12-month observation period after the initiation of therapy. Data from randomized clinical trials may present a picture that is overly optimistic regarding the effectiveness and tolerability of treatments, owing to careful patient selection as well as intensive patient surveillance and monitoring. Persons who participate in clinical trials generally differ from patients who eventually receive the medication in the community setting. Concomitant conditions, such as hypertension, ischemic heart disease, hyperlipidemia, and diabetes mellitus, were more common in our population than in participants of randomized clinical trials. The subjects who participated in the sildenafil clinical trials underwent an extensive diagnostic evaluation to determine the cause of erectile dysfunction. This evaluation included a complete medical history, relevant physical examination findings, and such procedures as an intracavernosal injection of a vasoactive drug, a RigiScan test of nocturnal penile tumescence, penile duplex ultrasonography, and endocrine testing.¹² In the general practice setting, pretreatment screening, evaluation, and selection for treatment with sildenafil is unlikely to be as rigorous.

In conclusion, the findings of our study suggest that sildenafil was rapidly and widely adopted for use as a treatment for erectile dysfunction in the managed care setting. Prescribing was not limited to specialists, and the population receiving the drug differed substantially from patients studied in published clinical trials. The example of how sildenafil was incorporated into general medical practice may serve as a model for how other newly marketed drugs that have the potential to affect patient lifestyle will be used.

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