

## Adherence to Paroxetine CR Compared With Paroxetine IR in a Medicare-eligible Population With Anxiety Disorders

*Matthew S. Keene, MD; Michael T. Eaddy, PharmD, PhD;  
Winnie W. Nelson, PharmD, MS; and Matthew W. Sarnes, PharmD*

### **Abstract**

There are many challenges in the pharmacologic management of elderly patients with anxiety disorders, including an increased sensitivity to drug effects, reduced drug metabolism, and socioeconomic barriers leading to poor medication adherence. As such, the purpose of this study was to evaluate differential rates of adherence between paroxetine controlled release (CR) and paroxetine immediate release (IR) in the treatment of anxiety disorders in a Medicare-eligible population. Patients aged 65 years or older initiating therapy with paroxetine CR or paroxetine IR with a diagnosis of anxiety were identified from the Integrated Healthcare Information Services National Managed Care Benchmark database from July 2001 to February 2004.

Logistic regression models were used to assess differences in 6-month adherence rates, controlling for differences in multiple background characteristics. Adherence was defined as having a minimum medication possession ratio of 80% over 180 days without evidence of a 15-day gap before 90 days of therapy. Of the 604 patients included in the study, 18% received paroxetine CR and 82% received paroxetine IR; comorbid anxiety and depression were present in 37.3% of patients. Overall, only 37.3% of patients adhered to therapy, with a greater percentage of patients adhering to paroxetine CR (45.0%) compared with paroxetine IR (35.6%). After controlling for background characteristics, patients receiving paroxetine IR were 38.7% less likely to adhere to therapy compared with patients receiving paroxetine CR ( $P = .0328$ ). When stratified by those with comorbid anxiety and depression, patients receiving paroxetine IR were 55.1% less likely to adhere to therapy compared with patients receiving paroxetine CR ( $P = .0292$ ).

This study demonstrates that antidepressant non-adherence is common in patients older than 65 years of age, with overall rates of nonadherence at 62.7% and patients receiving paroxetine IR having the lowest levels of adherence. Future work should assess differences in all available selective serotonin reuptake inhibitors while also directly assessing the economic impact of nonadherence in the elderly population.

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As the US population ages, careful consideration must be given to appropriate healthcare services for the elderly. By 2030, almost 20% of the US population is expected to be older than 65 years of age, and the number of Medicare enrollees is expected to nearly double to approximately 77 million.<sup>1,2</sup> Anxiety and depression are some of the most prevalent disorders in the elderly population, with 20% of patients older than the age of 65 experiencing symptoms of major depressive disorder or subsyndromal depression<sup>3</sup> and up to 20% of elderly patients currently experiencing some form of anxiety disorder.<sup>4,6</sup> In addition to their significant morbidity, the presence of these psychiatric disorders may diminish desired clinical and economic outcomes in the treatment of other comorbid conditions, such as coronary artery disease, diabetes, or congestive heart failure.<sup>7,8</sup>

The primary issues in the pharmacologic management of anxiety disorders in the elderly are efficacy, safety, tolerability, and appropriate adherence to therapy. Benzodiazepines have been the most widely studied class in anxiety and were considered the gold standard for treatment for many years.<sup>9,10</sup> However, there is substantial research highlighting the hazards of benzodiazepines in the elderly; recently, benzodiazepines were determined to be potentially inappropriate for use in the elderly, independent of diagnosis or condition.<sup>11</sup> Accordingly, benzodiazepines will not be covered under the Medicare Prescription Drug, Improvement, and Modernization Act.<sup>12</sup> Currently, selective serotonin reuptake inhibitors (SSRIs) are considered first-line therapy because of their ability to improve symptoms of anxiety and depres-

sion with improved safety and tolerability. Of the SSRIs available to treat anxiety disorders, paroxetine immediate release (IR) is the only agent that is indicated in all anxiety disorders, including post-traumatic stress disorder, obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, and social anxiety disorder. However, the effectiveness of any SSRI, including paroxetine IR, depends heavily on the likelihood of patients adhering to therapy. Early discontinuation of therapy, partial medication adherence, and therapy change are all patterns of utilization that have been negatively associated with treatment outcomes, such as a higher risk for relapse or recurrence of depression and less desirable economic outcomes in anxiety and depression.<sup>13-15</sup> Not only do SSRIs differ in efficacy pertaining to anxiety disorders but the likelihood of adhering to therapy is not equivalent across the SSRIs.

Paroxetine controlled release (CR) is the only SSRI with a delayed and slowed rate of absorption in the gastrointestinal tract. This may help minimize common SSRI-related side effects leading to early therapy discontinuation, which may be more significant in the elderly because this population tends to be more sensitive to pharmacotherapy-related adverse events.<sup>16,17</sup> Paroxetine CR has been shown to be both effective and safe in an elderly population, with dropout rates due to adverse events similar to placebo.<sup>18</sup> Paroxetine CR has been associated with a 28% lower risk of early discontinuation of therapy and a 16.5% lower risk of therapy change over a 6-month period in a managed care population when compared with IR SSRIs.<sup>19</sup> When Keene et al expanded the analysis to include newer SSRIs, such as escitalopram, similar results were found, with IR SSRIs having a significantly reduced likelihood of adherence over 6 months when compared with paroxetine CR, even when using a more stringent measure of adherence and a different population than previous studies.<sup>20</sup> In contrast, paroxetine IR, although chemically the same as paroxetine CR, has the lowest rates of adherence and highest rates of therapy change in comparison with all SSRIs.<sup>19-21</sup> The greatest disparity in rates of adherence

have actually been between paroxetine CR and paroxetine IR.<sup>19,20</sup> A head-to-head retrospective database investigation between the 2 agents found that patients receiving paroxetine CR were associated with a 40% reduction in the risk of therapy discontinuation over 6 months versus paroxetine IR.<sup>22</sup> Although these patterns of adherence are evident in the general population, there are no studies that directly compare paroxetine CR with paroxetine IR in the elderly. Such assessments are especially needed in elderly patients with anxiety, because these patients are particularly sensitive to the side effects of antidepressants.<sup>23,24</sup> As such, the purpose of this study was to evaluate differential rates of adherence between paroxetine IR and paroxetine CR in the treatment of anxiety disorders in a Medicare-eligible population.

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## METHODS

### Data Source

Medical and pharmacy data were abstracted from the Integrated Healthcare Information Services National Managed Care Benchmark database. This is a nationally representative database and includes data from 30 health plans covering more than 25 million lives.

### Sample Selection

Patients at least 65 years of age with a pharmacy claim for either paroxetine IR or paroxetine CR between July 1, 2001, and February 1, 2004, were identified in the database. The index date for patients was the date of the first SSRI prescription within this time period. To capture only those patients newly initiated on antidepressant therapy, patients were required to have no evidence of any antidepressant therapy in the 6-month period before their index date. In an attempt to isolate only the effect of the index medication on patient adherence, all patients with evidence of therapy change were excluded. Patients were also required to be continuously eligible for 6 months before and 6 months after their index date. Additionally, patients were required to have a coded diagnosis for an

**Table 1.** ICD-9-CM Codes

Inclusion diagnoses	Code
<b>Anxiety</b>	
Panic disorder without agoraphobia	300.01
Panic disorder with agoraphobia	300.21
Social phobia (social anxiety disorder)	300.23
Obsessive-compulsive disorder	300.3
Post-traumatic stress disorder	309.81
Acute stress disorder	308.3
Generalized anxiety disorder	300.02
Anxiety disorder not otherwise specified	300.00
Anxiety disorder due to general medical condition	293.89
<b>Depression*</b>	
Major depressive disorder, single episode	296.2
Major depressive disorder, recurrent episode	296.3
Neurotic depression	300.4
Depressive disorder not elsewhere classified	311.00

\*Depression was only included if comorbid with anxiety diagnosis. ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*.

anxiety disorder alone or an anxiety disorder with comorbid depression in the 6 months before or 6 months after their index date. Diagnoses were determined using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes, as listed in **Table 1**. Patients meeting all selection criteria were then placed into treatment cohorts based on their index prescription and followed for 6 months after their index date to assess 6-month adherence rates.

**Comorbidity Assessment**

To assess comorbidities across treatment cohorts, the Charlson Index with Dartmouth-Manitoba and Deyo modification was utilized.<sup>25,26</sup> This index contains 19 categories of comorbidities, primarily defined by ICD-9-CM diagnosis codes, with higher scores representing a higher burden of comorbidity. Charlson Index scores for this study were determined by the presence of various ICD-9-CM codes in the 6-month period before each patient’s index date.

Additional variables used to assess comorbidities in this period were: (1) a unique

count of disease states beyond those used to calculate the Charlson Index score; (2) the total number of prescriptions received; and (3) a unique count of prescription drug categories received, such as cardiovascular or antidiabetic medications.

**Adherence Metric**

Adherence to paroxetine IR and paroxetine CR was measured through a combination medication possession ratio (MPR) and early treatment discontinuation approach. The MPR was calculated using the continuous, multiple interval medications available methodology, as described by Steiner and Prochazka, which is the sum of the days’ supply of all antidepressant prescriptions in a specified time period divided by the total number of days in the time period.<sup>27</sup> In this analysis, the start and end dates of each prescription were the date the prescription was filled and the date corresponding to the date of the prescription fill plus the days’ supply, respectively. When prescriptions overlapped (ie, a patient acquired an additional prescription before the ending date of the preceding prescription), residual days were added to the ending date of the next prescription. Thus, patients were assumed to have consumed all medications acquired during the study period. As a result, some patients may have had MPR values above 100%, which were truncated at 100%. In previous studies, patients were deemed to have discontinued therapy if more than 15 days elapsed between prescriptions during the time period of interest.<sup>28</sup>

In this study, the MPR and the 15-day criteria were combined into one metric based on the Health Employer Data and Information Set (HEDIS) measures evaluating antidepressant medication management. The HEDIS performance measures indicate that patients should be receiving antidepressant therapy acutely for a minimum of 90 days and continuously for 180 days over a 231-day time frame (MPR = 78%).<sup>29</sup> Thus, patients in this study were deemed nonadherent with their antidepressants when their MPR was less than 80% over 180 days or if they had a 15-day gap between antidepressant prescriptions before 90 days of con-

tinuous therapy. Patients not having a 15-day gap before 90 days and remaining at least 80% adherent to therapy over the entire 180-day period were deemed adherent. The combination of the MPR metric and gaps in therapy to define adherence is a more stringent criterion than either method alone, and is thus less likely to misclassify nonadherent patients with inadequate days of therapy or significant gaps in treatment.

### Analysis of Outcomes

The primary variable of interest was the rate of adherence to the index medication for all patients, which was stratified by anxiety disorders and comorbid anxiety and depression. Logistic regression models were used to assess differences in the rates of adherence across the index medication cohorts, controlling for differences in age, sex, receipt of mental health specialty services, dose titration, insurance type, and comorbidity measures. Dose titration was defined as evidence of an increase in daily

SSRI dosage at some point after starting SSRI therapy. The alpha level of significance was set a priori at 0.05.

## RESULTS

### Sample

A total of 604 patients met the study inclusion criteria. The population was mostly women (66.6%), with a mean age of 71.4 years. This population had a high disease burden, with an average of 10.8 nonmental health diagnoses per patient and 13.6 nonmental health prescriptions per patient from 5.2 unique nonmental health prescription classes. Comorbid anxiety and depression was present in 37.3% of patients. These demographic characteristics are shown in **Table 2**.

Approximately 82% of all patients received paroxetine IR, whereas 18% received paroxetine CR. Demographic characteristics between the 2 treatment cohorts were similar. Patients initiating treatment with paroxetine CR were slightly more likely to be women

**Table 2.** Baseline Demographic Characteristics

Characteristic	Paroxetine IR (n = 495)	Paroxetine CR (n = 109)	Total (N = 604)
Age (years)	71.3	71.9	71.4
Women (%)	65.3	72.5	66.6
MH specialist visit (%)	9.5	11.0	9.8
Comorbid anxiety and depression diagnoses (%)	36.4	41.3	37.3
Charlson Index score (mean)	1.1	0.9	1.1
Non-MH diagnoses (mean)	10.9	10.7	10.8
Non-MH prescriptions (mean)	13.5	14.2	13.6
Unique non-MH prescription classes (mean)	5.2	5.5	5.2
Insurance type (%)			
HMO*	47.9	35.8	45.8
PPO <sup>†</sup>	24.9	39.5	27.5
Other <sup>‡</sup>	12.5	5.5	11.3
Independent	10.3	12.8	10.8
POS	4.4	6.4	4.8

\**P* = .0225 when comparing IR cohort with CR cohort.

<sup>†</sup>*P* = .0022 when comparing IR cohort with CR cohort.

<sup>‡</sup>*P* = .0416 when comparing IR cohort with CR cohort.

IR indicates immediate release; CR, controlled release; MH, mental health; HMO, health maintenance organization; PPO, preferred provider organization; POS, point of service.

**Table 3.** Likelihood of 6-month Adherence Versus Paroxetine CR in Patients With Anxiety

Parameter	Odds ratio	95% confidence interval	P value
<b>Anxiety disorders with or without depression</b>			
Paroxetine IR	0.613	0.391-0.961	.0328
Age	0.995	0.961-1.301	.7926
Women	0.899	0.621-1.289	.5717
MH specialty care	0.938	0.525-1.677	.8299
Presence of depression	0.989	0.689-1.419	.9518
Charlson Index score (mean)	1.015	0.874-1.177	.8446
Non-MH diagnoses (mean)	0.989	0.955-1.025	.5449
Non-MH prescriptions (mean)	1.017	0.989-1.046	.2449
Unique non-MH prescription classes (mean)	0.989	0.899-1.089	.8227
Titrate	2.317	1.582-3.393	<.0001
Insurance type*			
PPO	1.451	0.945-2.227	.0887
Other	0.821	0.440-1.532	.5359
Independent	1.599	0.908-2.818	.1042
POS	2.767	1.240-6.174	.0129
<b>Comorbid anxiety and depression only</b>			
Paroxetine IR	0.449	0.219-0.922	.0292
Age	1.002	0.944-1.064	.9514
Women	0.963	0.514-1.805	.9067
Charlson Index score (mean)	0.933	0.728-1.195	.5804
Non-MH diagnoses (mean)	1.015	0.959-1.074	.6140
Non-MH prescriptions (mean)	0.996	0.946-1.050	.8910
Non-MH prescriptions (mean)			
Unique non-MH prescription classes (mean)	1.009	0.843-1.208	.9187
MH specialty care	0.875	0.372-2.058	.7602
Titrate	2.428	1.290-4.570	.0060
Insurance type*			
PPO	1.688	0.813-3.506	.1601
Other	1.070	0.438-2.616	.8815
Independent	0.941	0.349-2.539	.9047
POS	1.784	0.471-6.751	.3942

\*Reference group = health maintenance organization.  
 CR indicates controlled release; IR, immediate release; MH, mental health; PPO, preferred provider organization;  
 POS, point of service.

and have more nonmental health-related medications, although no statistically significant differences were found (Table 2).

**Medication Adherence**

Overall, only 37.3% of patients were adherent with their index medication after 6 months, having maintained a minimum MPR of 80% with no gaps in therapy greater than 15 days in the first 90 days after initiation with the index medication.

A greater number of patients receiving paroxetine CR were deemed adherent with

therapy compared with patients receiving paroxetine IR (45.0% vs 35.6%, respectively). After adjusting for baseline covariates (age, sex, receipt of mental health specialty services, dose titration, and the comorbidity measures), patients receiving paroxetine IR were 38.7% less likely to adhere to therapy when compared with patients receiving paroxetine CR ( $P = .0328$ ), as shown in Table 3. When evaluating the subset of patients who had comorbid anxiety and depression ( $n = 225$ ), patients receiving paroxetine IR remained 55.1% less likely to adhere to ther-

apy compared with patients receiving paroxetine CR (paroxetine CR 48.9% vs paroxetine IR 33.9%).

## DISCUSSION

The objective of this study was to assess differential rates of adherence between paroxetine IR and paroxetine CR in the treatment of anxiety disorders with or without depression in a Medicare-eligible population. The rates of nonadherence observed in our results are higher than those reported by Eaddy et al and Sheehan et al in the general population, with 62.7% of patients deemed nonadherent after 6 months.<sup>19,22</sup> Although our rates of nonadherence are higher than previously reported, our study included an elderly population compared with a general, younger population.

Previous literature suggests that the elderly generally adhere less to medication compared with a younger population.<sup>17</sup> Elderly patients often have age-related factors affecting adherence, such as physical impairments (deterioration of vision or manual dexterity), psychosocial issues (cognitive impairment, inability to pay for medications), and an increased vulnerability to drug effects, although reasons for nonadherence could not be assessed as part of our study.<sup>17</sup> These higher rates of nonadherence may also reflect the sensitivity that elderly patients have to pharmacotherapy-related side effects.

In the elderly, there is a narrower index between therapeutic effect and drug toxicity, which may be manifested as increased sensitivity to adverse effects.<sup>17</sup> Previous work showed dropout rates due to adverse events for paroxetine CR were similar to placebo.<sup>30</sup> In our study, elderly patients receiving paroxetine IR were almost 40% less likely to adhere to therapy than patients receiving paroxetine CR, mirroring the results observed by Sheehan et al, who also found that patients receiving paroxetine CR were 40% less likely to discontinue therapy over 6 months compared with paroxetine IR in a general population.<sup>22</sup> These results further support work suggesting that adherence

to therapy is not equivalent across the SSRIs.<sup>19,20</sup> Because both treatment cohorts in this study were drawn from a population with commercial insurance coverage and similar demographic characteristics, differences in these factors are less likely to have driven the differential rates of adherence between paroxetine IR and paroxetine CR. Rather, tolerability or efficacy of the respective therapy may play a larger role.

Poor adherence to antidepressant therapy has severe clinical and economic consequences; it has been demonstrated that increasing the length of antidepressant therapy by 30 days decreased the risk of all-cause hospitalization by 14%.<sup>31</sup> It is possible that the benefits of adherence to therapy in an elderly population are more pronounced. Col et al found that 11% of hospital admissions in patients 65 years and older were the result of nonadherence,<sup>32</sup> whereas Chan et al found that 26% of hospital admissions in patients 75 years and older were the result of nonadherence or drug discontinuation.<sup>33</sup> This work supports studies demonstrating that patients who discontinue antidepressant therapy before the minimum recommended duration of 4 to 6 months or have only partial medication adherence during therapy utilize greater healthcare resources and cost more per month than patients with continuous uninterrupted therapy.<sup>28,34</sup> Given the clinical and economic implications of nonadherence and the low rates seen in our study, there is a need for improved medication management in the elderly. Tools such as adherence aids (ie, weekly pillboxes and automated refill reminders) and collaborative care or disease management programs may be beneficial in this patient population.<sup>35,36</sup>

Although our study indicates that paroxetine CR is associated with improved 6-month adherence to therapy, there are limitations that should be addressed. First, the retrospective study design restricts the ability to draw direct causal relationships between antidepressant therapy and adherence. Because patients were not randomized to treatment cohorts, it is possible that adherence was a result of factors that cannot be controlled in a retrospective study design. In an attempt to minimize this bias, back-

ground characteristics, such as age, sex, comorbidities, and mental health specialty services, were controlled in the logistic regression model; however, residual confounding cannot be ruled out.

Second, the use of administrative claims data may not have fully captured all eligible patients. The accuracy of claims data relies on the accuracy of *ICD-9* coding for anxiety with or without depression. Because undercoding is common in depression and anxiety, it is possible that patients were misclassified, which may have weakened the association between antidepressant utilization and adherence.<sup>37</sup> This is partly a result of the notion that patient diagnoses, such as comorbid anxiety and depression, could be correlated to differential rates of adherence and worse clinical outcomes.<sup>38</sup> However, based on the distribution of background covariates, any effect resulting from this association would negatively influence paroxetine CR, because this product was associated with a higher rate of comorbid anxiety and depression.

Despite the discussed limitations, this study highlights the very low rate of antidepressant adherence in the elderly in a naturalistic setting and draws attention to the potential improvement in adherence with paroxetine CR compared with paroxetine IR. These results are timely and important when considering the large number of elderly patients who currently receive and may begin therapy for anxiety and/or depression. With the implementation of the Medicare Part D prescription drug coverage in January 2006, Medicare prescription drug expenditures are expected to jump from approximately \$5 billion annually to more than \$70 billion annually.<sup>2</sup> Because the purpose of the drug benefit is to provide prescription coverage to millions of Medicare beneficiaries who may not have previously had any, a surge in the number of patients newly initiated on antidepressant therapy may be expected. Given the number of patients potentially receiving antidepressant therapy, a 38.7% lower likelihood of adherence with paroxetine IR versus paroxetine CR has clear relevance if the economic impact of nonadherence is manifested as seen in general commercial populations, because pa-

tients who are nonadherent incur higher medical costs than adherent patients.<sup>22,34</sup> Work by Eaddy et al found that nonadherent patients incurred approximately \$1150 more in annual medical expenses than adherent patients.<sup>34</sup> Although our study is one of the first studies investigating differential medication adherence in the elderly, further work is needed to validate these results. Future work should assess differences in all available SSRIs while directly assessing the economic impact of nonadherence in the elderly.

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**CONCLUSION**

Approximately 62.7% of patients older than 65 years of age with anxiety disorders initiating therapy with paroxetine IR or paroxetine CR were nonadherent over a 6-month period, with patients receiving paroxetine IR being 38.7% less likely to adhere than patients receiving paroxetine CR. Patients with comorbid anxiety and depression receiving paroxetine IR were even less likely to adhere to therapy compared with patients receiving paroxetine CR.

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