Generic Initiation and Antidepressant Therapy Adherence Under Medicare Part D

Yuhua Bao, PhD; Andrew M. Ryan, PhD; Huibo Shao, MS; Harold Alan Pincus, MD; and Julie M. Donohue, PhD

Objectives: To assess the effect of initiating antidepressant therapy with a generic prescription on adherence to antidepressant therapy among Medicare patients. A second objective is to assess how the effect might be moderated by the Medicare Part D coverage gap.

Study Design and Methods: Adherence to antidepressant therapy was measured by (a lack of) disruption in medication use defined by a gap of 30 days or more in antidepressant possession and monthly days of possession, both measured over 180 days since antidepressant initiation. We used a 5% random sample of Medicare fee-for-service beneficiaries who received a new depression diagnosis in the first half of 2007 and initiated antidepressant therapy within 60 days (n = 16,778). We estimated a Cox proportional hazard model for antidepressant disruption and a mixed-effects linear model for monthly possession. All analyses were stratified by 4 cohorts defined by Part D low-income subsidy (LIS) status and Medicare entitlement (aged vs disabled).

Results: Generic initiation was associated with improved adherence among all 4 cohorts, with a stronger effect among the non-LIS patients. Hazard ratios for antidepressant disruption ranged from 0.71 (95% confidence interval [CI], 0.53-0.96) among non-LIS, disabled patients to 0.88 (95% CI, 0.79-0.98) among LIS, aged patients. Generic initiation was associated with increases in days of monthly possession in all 4 cohorts and an additional benefit during the coverage gap for non-LIS patients.

Conclusions: Generic initiation can be an important tool to improve adherence to antidepressant treatment among Medicare patients and to mitigate the negative effects of the Part D coverage gap.

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For author information and disclosures, see end of text.

Antidepressants are among the most prescribed drugs for US adults.[1] Among people 65 years or older, 14% use antidepressants annually for depression, anxiety, or another indication.[2] While adherence to antidepressants is critical to realizing the effectiveness of antidepressant treatment,[3,4] around 40% of Medicare managed care patients discontinue their antidepressant treatment prematurely.[5] High out-of-pocket costs due to lack of drug coverage or high cost sharing has been shown to decrease drug adherence in most populations,[6] including Medicare beneficiaries using antidepressant medication.[7]

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Generic antidepressants are now widely available.[8] By 2007, most major brands of second-generation antidepressants had generic equivalents in the US market. Generic use has the potential to improve adherence to antidepressant therapy because patient out-of-pocket costs for generics are nearly always much lower than they are for brands.[9] For example, for patients receiving Medicare prescription benefits in 2011, the median copayment was $7 for generics, $42 for preferred brands, and $78 for nonpreferred brands.[10] Choice of generic or brand name is partly a function of provider preferences.[11] When a branded drug is prescribed in absence of a "dispense as written" request by the prescriber or the patient, patients often receive a generic equivalent because of state mandates of generic substitution[12] or pharmacist discretion. The generic (vs branded) status of the first prescription is likely highly influential in determining generic or branded drug use throughout the course of treatment and therefore may have important implications for patient adherence to chronic medication therapy.

The cost advantage of generics has greater implications under Medicare's current prescription drug benefit (Part D) than under a traditional insurance plan because of the Part D coverage gap. For example, in 2007 (the study year), under most plans, patients whose total Part D–covered drug spending reached $2510 were responsible for 100% of drug costs until their total spending reached $5726, or until the start of 2008. An estimated 3.4 million beneficiaries (about 14% of all Part D enrollees) reached the coverage gap in 2007.[13] While the Affordable Care Act will take steps to gradually close the coverage gap over the 10 years starting in 2011, in the near term, differences in out-of-pocket costs between branded and generic

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Take-Away Points

Encouraging prescribers to initiate antidepressant treatment with a generic drug has the potential to improve antidepressant adherence among Medicare patients.

- Starting patients with generics had benefits for antidepressant adherence by lowering out-of-pocket costs for all patients and by mitigating the effect of the Part D coverage gap faced by patients not receiving low-income subsidies.
- Managed care organizations may target prescriber drug choice behaviors to further improve antidepressant adherence and effectiveness of antidepressant treatment among its members.

antidepressants will remain greater during the coverage gap than otherwise.

In this study, we assessed the effects of initiating antidepressant treatment with a generic versus a branded prescription (generic initiation) on adherence to antidepressant therapy for the treatment of depression. Our study contributes to the literature by examining both the effect of generic initiation by itself and how the effect might be moderated by the presence of the Medicare Part D coverage gap.

METHODS

Data

We used data from a 5% random sample of beneficiaries with depression in 2006 and 2007 from the Medicare Chronic Condition Data Warehouse.[14] Files used in this study included carrier claims and the Part D Prescription Drug Event file. We also used the Beneficiary Summary File and Chronic Condition Summary File to derive demographic and comorbidity information for beneficiaries.

Study Sample

Our study population was Medicare fee-for-service patients who experienced a new episode of depression and subsequently initiated antidepressant therapy within 60 days of the new depression diagnosis. This is a population with a clear clinical indication for depression treatment. To be included in the analysis, all beneficiaries were required to be continuously enrolled in Medicare Parts A and B throughout 2006 and 2007. Because Part D had an enrollment deadline of May 11 in 2006, we further required beneficiaries to be continuously enrolled in Part D from July 1, 2006, to December 31, 2007.

To identify patients experiencing a new episode of depression, we first identified for each patient the first physician service claim between January 1 and June 30, 2007, that had major depression, depressive disorder not elsewhere classified, or dysthymia as a primary or secondary diagnosis (*International Classification of Diseases, Ninth Revision* codes 296.2x, 296.3x, 311x, and 300.4x) (the index diagnosis). We further excluded patients who had any physician claim with a depression diagnosis or antidepressant use during the 6 months prior to the index diagnosis. We then restricted the sample to patients who filled an antidepressant prescription within 60 days of the index date. The resulting study sample contained patients who initiated antidepressant therapy no later than July 4, 2007, to allow for follow-up data covering 180 days after initiation for every patient. We excluded 111 patients who had missing Part D benefit phase information. We also excluded a small number of beneficiaries who were entitled to Medicare because of end-stage renal disease.

More than half of patients in the study sample received the Part D low-income subsidy (LIS) and thus were not subject to the coverage gap. Among patients not receiving LIS, we excluded patients who were already in the coverage gap by the time they initiated antidepressant therapy (n = 434), since these patients faced very different cost sharing compared with patients who transitioned into the coverage gap after antidepressant initiation. Among non-LIS patients who transitioned into the coverage gap during the 180 days, about 20% spent through the coverage gap later in 2007 and transitioned to the catastrophic coverage phase in which they had almost complete coverage. A recent study of a depression cohort found that patients who eventually attained catastrophic coverage did not change their medication use while in the coverage gap.[15] We thus excluded these patients (n = 431) in our main analysis. In a sensitivity analysis, we included both types of patients to examine the robustness of our findings. Our main analytic sample included 16,778 beneficiaries.

We identified 4 distinct patient cohorts defined by their Medicare entitlement status (aged vs disabled) and Part D LIS status. Disabled beneficiaries differ in both socioeconomic status and complexity of healthcare needs from aged beneficiaries. Patients receiving LIS are either Medicare-Medicaid dual enrollees or have limited income or resources[16]; as shown below, they also have more comorbid conditions. We thus chose not to treat the LIS patients as a "control" cohort for the non-LIS patients (since their baseline trends in medication may not be comparable), but instead stratified all of our analysis by the 4 patient populations.

We used the Multum Lexicon drug classification system[17] to identify antidepressants (and whether a given prescription was generic or branded) based on the National Drug Code. We used drug-dispensing date and days of supply to determine time intervals during which a patient was in possession

of antidepressants. When 2 or more intervals overlapped, we counted the overlapping period only once.

Main Outcome Measures

We created 2 measures of antidepressant adherence. The first measure is disruption in antidepressant therapy during the 180 days after initiation, equal to 1 if there was a gap in antidepressant possession of 30 days or longer and 0 otherwise. Patients who switched medication during the 180 days were considered adherent (ie, no disruption) as long as they did not experience a gap of 30 days or more. A follow-up period of 180 days was based on depression treatment guidelines that recommend minimum length of pharmacotherapy during acute and continuation phases of treatment.[3,4,18] The 30-day gap was defined so that patients who retained antidepressants from previous fills or who had a washout period between medication changes would not be incorrectly classified as nonadherent.[19]

The second measure, monthly days of antidepressant possession, is defined as the number of days in each of the 6 months following antidepressant initiation that the patient was in possession of antidepressants. We chose a monthly measure of possession (rather than the typical medication possession ratio over 180 days) because the monthly measure allows us to examine the dynamics of antidepressant use in relationship to the onset of the coverage gap.

Independent Variables

Our primary independent variable was the generic/brand status of the first prescription. Of all the branded antidepressant initiations in our sample, 83% were 1 of 3 antidepressants that did not yet have a generic equivalent on the US market in 2007: Lexapro (escitalopram, a selective serotonin reuptake inhibitor [SSRI], accounting for 44% of all branded initiations), Cymbalta (duloxetine, a serotonin and norepinephrine reuptake inhibitor; 20%) and Effexor XR (venlafaxine XR, a serotonin and norepinephrine reuptake inhibitor; 19%). While our main analysis included all classes of antidepressants, we conducted a sensitivity analysis by including only patients who initiated their treatment with a generic or branded SSRI.

For non-LIS patients, whose Part D coverage includes a coverage gap, a second independent variable of interest was an indicator of whether the patient was in the coverage gap at a given time. In analyses of both outcomes, this indicator is time varying because patients may transition into the coverage gap during the follow-up.

Statistical Analysis

For disruption in antidepressant therapy, we estimated a Cox proportional hazard model of time to disruption. For non-LIS patients, in addition to generic initiation, independent variables included Part D benefit phase (coverage gap vs before the coverage gap) and an interaction between generic initiation and coverage gap. This allowed us to examine whether the effect of generic initiation was stronger as patients experienced the coverage gap. We conducted tests of the proportional hazard assumption based on Schoenfeld residuals.[20]

For monthly days with antidepressant possession, we estimated a mixed-effects linear model using data at the patient-month level, with a patient-level random intercept to account for correlations between multiple observations clustered within a given patient. Generic initiation was the primary independent variable. The models estimated among the non-LIS cohorts also included dichotomous indicators of number of complete months that a patient had been in the coverage gap, which ranged from 1 to 5. This was to allow the effect of coverage gap to differ with the length of time spent in the coverage gap. Interaction terms between generic initiation and each of the coverage gap month indicators were also included. To control for time patterns in antidepressant use that were independent from the effects of generic initiation and experience of the coverage gap, we included ordinal indicators of months following antidepressant initiation.

In all analyses, we controlled for patient demographics (age, sex, race/ethnicity), measures of patient disease burden (indicators of 9 comorbid chronic condition categories based on the Chronic Condition Data Warehouse definition[21] and the natural log of total prescription drug spending in 2007), and the specialty of the clinician associated with the index clinical encounter that established the new depression diagnosis (primary care, mental health specialty, or other medical specialty).

RESULTS

Of the 16,778 patients in our study sample, 65% received LIS in 2007 compared with a national average of 36%,[16] reflecting the substantially lower socioeconomic status of patients with depression (**Table 1**). Close to 50% of LIS patients were entitled to Medicare because of disability rather than old age compared with 11% among the non-LIS sample. The LIS sample was less likely to be white and had a greater number of comorbid conditions. Total prescription drug costs in 2007 for the 2 cohorts receiving LIS were 2 to 3 times higher than those for the non-LIS cohorts with the same entitlement status. Patients receiving LIS were also more likely to have received their depression diagnosis from a mental health specialist and less likely to have received it from a primary

Table 1. Descriptive Sample Statistics

Characteristics	LIS		Non-LIS	
	Aged (n = 5679)	Disabled (n = 5210)	Aged (n = 5243)	Disabled (n = 646)
Age, y, mean (SD)	78.9 (8.3)	49.0 (9.9)	77.9 (7.6)	53.6 (8.5)
Female sex, n (%)	4716 (83.0)	3393 (65.1)	4250 (81.1)	400 (61.9)
Race/ethnicity, n (%)				
White, non-Hispanic	4668 (82.4)	4195 (80.7)	5080 (97.0)	569 (88.1)
Black, non-Hispanic	560 (9.9)	679 (13.1)	83 (1.6)	45 (7.0)
Hispanic	272 (4.8)	177 (3.4)	32 (0.6)	10 (1.6)
Other race/ethnicity	166 (2.9)	147 (2.8)	43 (0.8)	22 (3.4)
No. of comorbid conditions,[a] mean (SD)	2.9 (1.5)	1.3 (1.3)	2.1 (1.4)	1.0 (1.2)
Total prescription costs in 2007, $, mean (SD)	5330.3 (4095.8)	7101.3 (7476.2)	2674.8 (2591.9)	2716.0 (4221.0)
Diagnosing clinician, n (%)				
Primary care	3732 (65.7)	2894 (55.6)	3930 (75.0)	387 (59.9)
Mental health specialty	1457 (25.7)	1506 (28.9)	819 (15.6)	179 (27.7)
Other specialty	490 (8.6)	810 (15.6)	494 (9.4)	80 (12.4)
Generic (vs branded) initiation,[b] n (%)	3862 (68.0)	3225 (61.9)	3581 (68.3)	425 (65.8)
Experienced coverage gap during 180 days, n (%)	—	—	1567 (29.9)	164 (25.4)
Disruption in antidepressant therapy over 180 days,[c] % (95% CI)	29.3 (28.1-30.4)	31.4 (30.2-32.7)	35.2 (33.8-36.5)	39.3 (35.6-43.1)
Monthly possession of antidepressants, days, (95% CI)				
First month	29.7 (29.6-29.7)	29.7 (29.7-29.8)	29.7 (29.7-29.8)	29.8 (29.7-29.9)
Second month	23.9 (23.6-24.2)	22.7 (22.4-23.0)	22.5 (22.2-22.8)	21.5 (20.6-22.4)
Third month	23.5 (23.3-23.8)	23.0 (22.7-23.3)	22.6 (22.3-22.9)	22.0 (21.1-22.9)
Fourth month	22.8 (22.6-23.1)	22.4 (22.0-22.7)	21.3 (21.0-21.7)	20.1 (19.2-21.0)
Fifth month	22.7 (22.5-23.0)	22.2 (21.9-22.5)	21.2 (20.9-21.5)	20.0 (19.0-20.9)
Sixth month	22.6 (22.3-22.9)	21.8 (21.5-22.1)	20.8 (20.5-21.2)	19.0 (18.1-20.0)

CI indicates confidence interval; LIS, low-income subsidy; SD, standard deviation.
[a]The number of comorbid conditions is a count of the presence of the following conditions: Alzheimer's disease or dementia, cardiovascular or cerebrovascular conditions (atrial fibrillation, heart failure, ischemic heart disease, stroke/transient ischemic attack), chronic kidney disease, chronic obstructive pulmonary disease, diabetes, eye conditions (cataract or glaucoma), hip fracture, osteoporosis/rheumatoid arthritis/osteoarthritis, and cancer (breast, colorectal, prostate, lung, endometrial). All conditions were defined based on Chronic Condition Warehouse rules based on *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes in Medicare claims.
[b]Generic initiation is 1 (0 otherwise) if the prescription filled at the initiation of the therapy was a generic (vs branded) antidepressant.
[c]Disruption in antidepressant therapy was defined as a gap of 30 days or longer in the possession of antidepressants.

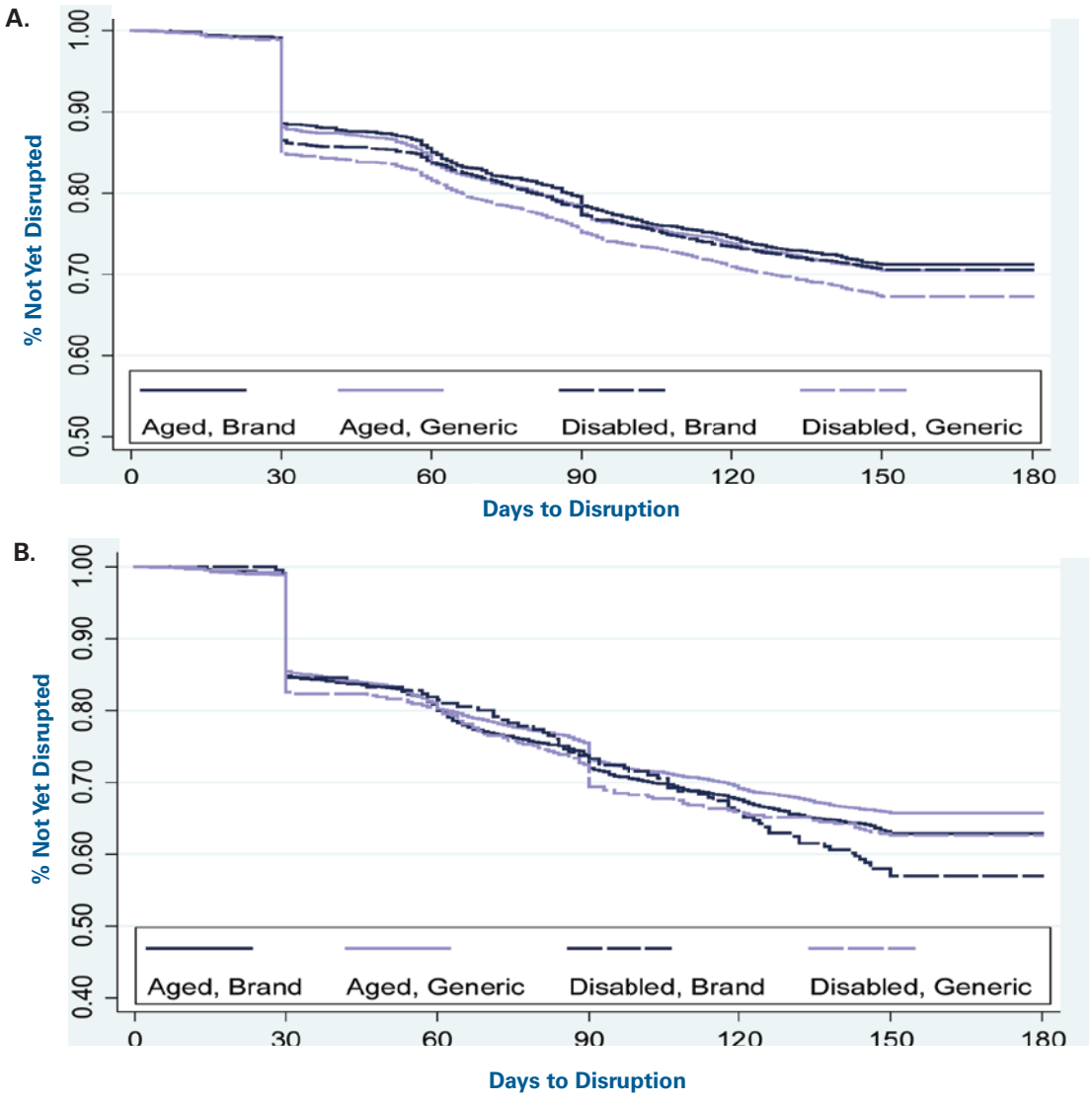
care clinician. Of the non-LIS patients, 30% of the aged transitioned into the coverage gap during the 180-day follow-up compared with 25% of the disabled.

The rate of generic initiation ranged from 62% to 68% across the 4 patient cohorts. Of all patients with generic initiation, 11.6% switched to a branded antidepressant within 180 days, while 30.6% of patients with an initial branded antidepressant switched to generics, indicating strong persistence of generic (or branded) choice throughout treatment episode and significance of the initial drug choice. Mean out-of-pocket cost for a 30-day supply of antidepressants was substantially lower for generic versus branded antidepressant initiations: for LIS patients, it was $1.00 if generic compared with $3.71 if branded; for non-LIS patients, it was $6.78 if generic compared with $35.78 if branded.

Antidepressant Disruption

Rate of disruption in antidepressant therapy ranged from 29.3% (95% confidence interval [CI], 28.1%-30.4%) among the LIS, aged patients to 39.3% (95% CI, 35.6%-43.1%) among the non-LIS, disabled patients (Table 1). Figures 1A and 1B show unadjusted Kaplan-Meier survival curves by patient disability status and generic status of first antidepressant for LIS and non-LIS patients, respectively. Both

■ **Figure 1.** Survival Curves for Disruption in Antidepressant Therapy by Disability Status and Generic Status of First Antidepressant (A) With the Low-Income Subsidy and (B) Without the Low-Income Subsidy



LIS indicates low-income subsidy.

figures show a sharp increase in disruption (decline in the survival curves) at 30 days after antidepressant initiation. Among the LIS patients (Figure 1A), a greater proportion of disabled patients with generic initiation had a disruption in antidepressant therapy at 30 days; their survival curve was below those of the other 3 groups for the rest of the follow-up. Among the non-LIS patients (Figure 1B), survival curves for all 4 groups traced each other closely until around the 120th day, when disabled patients who initiated therapy with a branded antidepressant started to experience a greater risk of disruption.

Tests of the proportional hazard assumption indicated no evidence of violation of the assumption in any of the Cox models we estimated. Results (Table 2) show that generic initiation was associated with a lower hazard of treatment disruption across all 4 cohorts. Among LIS patients, the hazard ratio (HR) for generic initiation was 0.88 (95% CI, 0.79-0.98; P = .020) for the aged and 0.84 (95% CI, 0.75-0.93; P = .001) for the disabled. For the non-LIS patients, HRs for generic initiation were lower: 0.78 (95% CI, 0.70-0.87; P <.001) among the aged and 0.71 (95% CI, 0.53-0.96; P = .025) among the disabled. The HR associated with the

Table 2. Disruption in Antidepressant Therapy[a]

	Hazard Ratio (95% CI); *P*			
	LIS		Non-LIS	
Variable	Aged	Disabled	Aged	Disabled
Generic initiation	0.88 (0.79-0.98); *P* = .020	0.84 (0.75-0.93); *P* = .001	0.78 (0.70-0.87); *P* <.001	0.71 (0.53-0.96); *P* = .025
Coverage gap (vs before the coverage gap)	—	—	1.27 (0.98-1.65); *P* = .075	2.05 (1.18-3.55); *P* = .010
Generic initiation × coverage gap	—	—	0.92 (0.65-1.30); *P* = .621	0.70 (0.27-0.79); *P* = .455

CI indicates confidence interval; LIS low-income subsidy.
[a]Results are based on Cox proportional hazard models that controlled for patient demographics (age, sex, race/ethnicity), measures of patient disease burden (indicators of 9 comorbid conditions based on Chronic Condition Warehouse definition and the natural log of total prescription drug spending in 2007), and the specialty of the diagnosing clinician associated with the index outpatient visit (primary care, mental health specialty, or other medical specialty).

coverage gap was 2.05 (95% CI, 1.18-3.55; *P* = .010) among the non-LIS, disabled patients. The HRs for the interaction between generic initiation and the coverage gap were below 1 in both analyses but not statistically significant.

Monthly Antidepressant Possession

As depicted in Figures 2A and 2B, all 4 cohorts experienced sharp declines in monthly possession from the first to the second month. The non-LIS, disabled patients with a branded initiation began to experience a sharper decline in possession in the fourth month, leading to 2 to 4 fewer days of possession in month 6 compared with the other 3 cohorts (Figure 2B).

Based on the mixed-effects models (Table 3), generic initiation was associated with a small but statistically significant increase in monthly possession in all 4 cohorts: 0.6 days (95% CI, 0.2-1.0; *P* = .003) for the LIS, aged patients and 0.7 days (95% CI, 0.3-1.1; *P* <.001) for the LIS, disabled patients; 0.9 days (95% CI, 0.5-1.4; *P* <.001) for the non-LIS, aged patients and 2.1 days (95% CI, 0.7-3.4; *P* <.001) for the non-LIS, disabled patients. For the non-LIS, aged patients, experiencing the coverage gap was not significantly associated with reductions in monthly possession except for the third month in the coverage gap (1.1 fewer days, 95% CI, –2.2 to 0.0; *P* = .045). For the disabled, however, the coverage gap had a significant effect while patients were experiencing the second complete month (–4.1 days, 95% CI, –6.6 to –1.7; *P* = .001) and third complete month (–4.1 days, 95% CI, –7.2 to –1.0; *P* = .001) in the coverage gap. Generic initiation was associated with an additional increase in monthly possession among non-LIS patients experiencing the coverage gap. For example, for disabled patients, generic initiation was associated with an additional 4.1 days (95% CI, 0.4-7.8; *P* = .032) of possession when patients were experiencing the second month in the coverage gap.

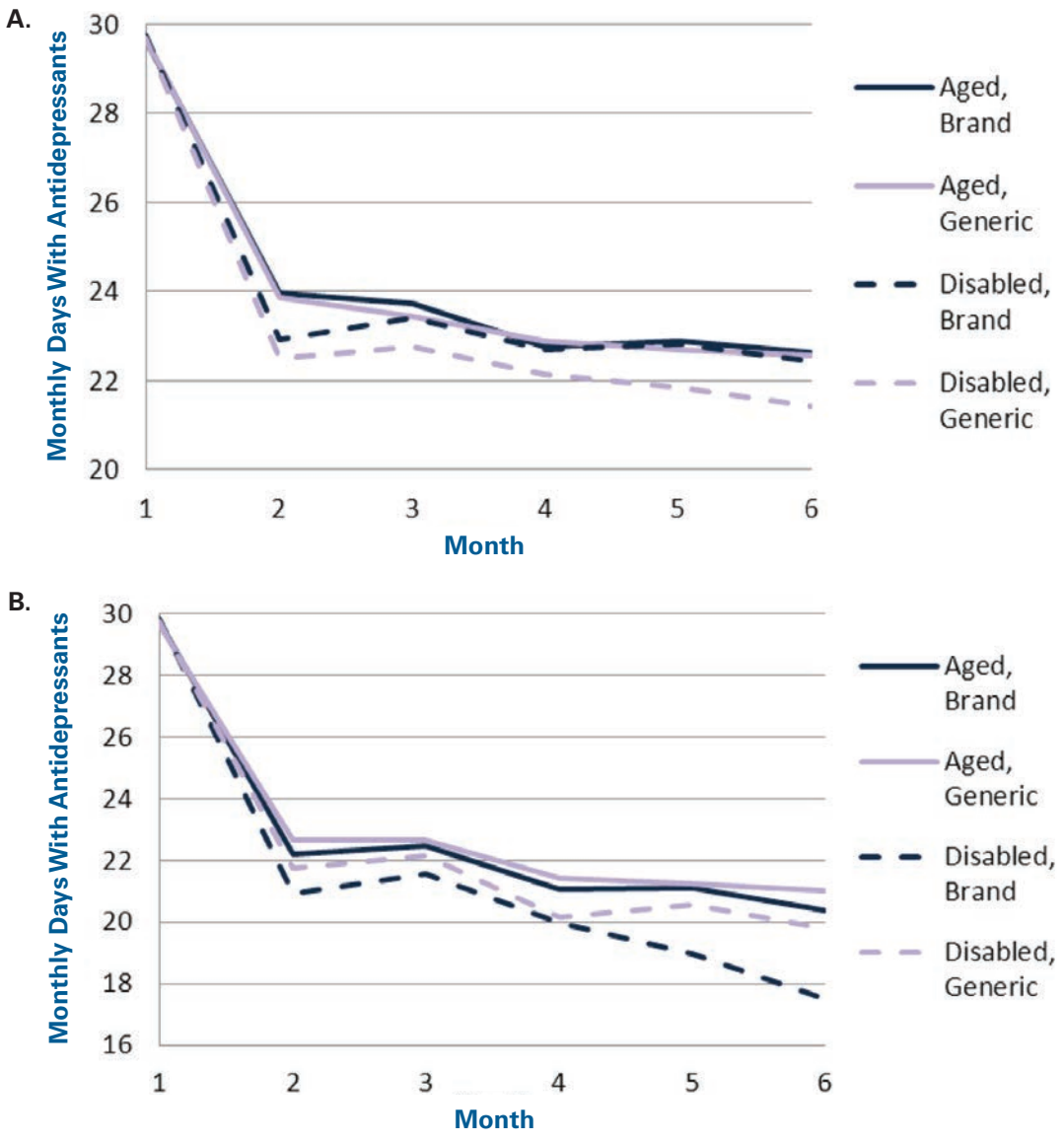
Sensitivity analyses that included non-LIS patients who were experiencing the coverage gap at antidepressant initiation and those who later transitioned into catastrophic coverage yielded consistent results regarding the effect of generic initiation for both outcomes, although effects of the coverage gap on adherence were slightly weaker in this larger sample. Sensitivity analysis that was limited to SSRI initiations only estimated comparable effect sizes for generic initiation with larger CIs.

DISCUSSION

Across 4 cohorts of fee-for-service Medicare beneficiaries newly diagnosed with depression and treated with antidepressants in 2007, we found that initiating the therapy with a generic antidepressant was consistently associated with increased medication adherence. This effect was stronger among the 2 non-LIS cohorts and strongest among the non-LIS, disabled cohort. Generic initiation increased the likelihood of monthly antidepressant possession while non-LIS patients were experiencing the Part D coverage gap.

Previous studies have linked out-of-pocket cost differentials between generic and branded medications to substantially increased adherence among patients starting with a generic medication for several chronic medical conditions.[9] Our results suggest that beneficial effects of generic use apply to antidepressant therapy as well. However, such benefits may vary across patient populations. For example, a recent study of commercially insured patients did not find generic initiation to be associated with a greater likelihood of refill of the initially prescribed antidepressant.[22] The consistent benefits of generic initiation found in our study, regardless of LIS status, may reflect the lower socioeconomic status of depressed Medicare beneficiaries and their greater sensitivity to cost differentials between generic and branded drugs. Our

■ **Figure 2.** Monthly Days of Antidepressant Possession by Disability Status and Generic Status of First Antidepressant (A) With the Low-Income Subsidy and (B) Without the Low-Income Subsidy



LIS indicates low-income subsidy.

findings thus lend strong support for generic initiation as a means to improve antidepressant adherence among Medicare patients.

Our findings also suggest that while the Part D coverage gap may be detrimental to antidepressant adherence, the benefits of generic initiation may mitigate the negative effects. Disabled patients not receiving LIS may be especially vulnerable to increased out-of-pocket cost during the coverage gap, and they appear to benefit most from the protective effect of generic initiation.

About half of the disruption in antidepressant therapy across all patient cohorts occurred at 30 days after initiation, which, for most patients, also marked the end of the first prescription. Myriad factors may underlie the dramatic decline in adherence by the end of the first month. Beneficiaries may discontinue medication due to lack of response, side effects, and/or a lack of continued medication management (dose titration, medication switch, or augmentation). Physicians may not have adequately educated patients on antidepressant treatment when prescribing the medication and/or may not

Table 3. Monthly Days of Antidepressant Possesion[a]

	Incremental Days (95% CI); *P*			
	LIS		Non-LIS	
Timeline	Aged	Disabled	Aged	Disabled
Generic initiation	0.6 (0.2, 1.0); *P* = .003	0.7 (0.3, 1.1); *P* <.001	0.9 (0.5 to 1.4); *P* <.001	2.1 (0.7 to 3.4); *P* = .002
First month in coverage gap			0.1 (–0.7 to 0.8); *P* = .885	–0.6 (–2.7-1.5); *P* = .584
Second month in coverage gap			0.1 (–0.8 to 0.9); *P* = .896	–4.1 (–6.6 to –1.7); *P* = .001
Third month in coverage gap			–1.1 (–2.2 to 0.0); *P* = .045	–4.1 (–7.2 to –1.0); *P* = .009
Fourth month in coverage gap			–1.2 (–2.8 to 0.3); *P* = .116	–3.8 (–7.7 to 0.2); *P* = .062
Fifth month in coverage gap			–0.4 (–2.8 to 2.0); *P* = .749	0.7 (–4.6 to 6.0); *P* = .792
Generic initiation × first month in coverage gap			1.0 (0.0-2.0); *P* = .047	–1.9 (–5.0 to 1.2); *P* = .224
Generic initiation × second month in coverage gap			0.8 (–0.4 to 1.9); *P* = .177	4.1 (0.4-7.8); *P* = .032
Generic initiation × third month in coverage gap			1.4 (0.0-2.8); *P* = .047	4.4 (–0.2 to 9.1); *P* = .063
Generic initiation × fourth month in coverage gap			2.4 (0.4-4.3); *P* = .017	2.9 (–3.0 to 8.9); *P* = .333
Generic initiation × fifth month in coverage gap			0.3 (–2.9 to 3.6); *P* = .847	1.8 (–6.5 to 10.1); *P* = .676

CI indicates confidence interval; LIS low-income subsidy.
[a]Results are based on mixed-effects linear models at the patient-month level, with a patient-level random intercept. All models controlled for patient demographics (age, sex, race/ethnicity), measures of patient disease burden (indicators of 9 comorbid conditions based on Chronic Condition Warehouse definition and the natural log of total prescription drug spending in 2007), and the specialty of the diagnosing clinician associated with the index outpatient visit (primary care, mental health specialty, or other medical specialty).

have followed up with sufficient intensity. Medication management accompanied by systematic clinical assessment may be important to further improve adherence.[23]

In our unadjusted analysis of the LIS cohorts, disabled patients with generic initiation were shown to have worse adherence compared with disabled patients with branded initiation, which was inconsistent with findings of the adjusted analysis. Disabled patients receiving LIS were particularly vulnerable to socioeconomic disadvantages that were positively associated with generic initiation, but at the same time, negatively associated with adherence. In an unadjusted analysis, confounding by these factors may have outweighed the effect of generic initiation.

One limitation of our study is that we are unable to measure all of the clinical characteristics of patients that may influence choice of branded versus generic antidepressant. For example, clinicians may have selectively prescribed branded antidepressants to patients whom they perceived as having a greater risk of nonadherence if started on older generic drugs. However, we do not believe this is likely to bias our estimates, for several reasons. First, recent evidence shows very similar efficacy and side effect profiles among second-generation antidepressants (including the branded drugs seen in this study).[24] For a given patient who is treatment naïve, clinicians have little basis for predicting whether one antidepressant would be more effective or tolerable than another, especially among the second-generation classes.[25] Thus, clinician choice of branded versus generic initiation based on clinical characteristics may be quite limited. Second, previous studies have consistently shown that provider preferences are a much stronger determinant of medication choice than are patient clinical needs; generic initiation status may largely reflect prescriber and patient familiarity with the drug chosen and affordability to the patient.[26-28]

Other limitations include the following. Our data are for Medicare fee-for-service patients only; our findings may not extend to Medicare managed care patients. Like all studies that use claims data for adherence research, we based inferences on antidepressant possession, not drugs taken. As a result, the sharp decline in adherence seen at the end of the

first month reflects failures to renew 30-day prescriptions and should not be interpreted as nonadherence at exactly 30 days after initiation. Our measures of antidepressant adherence reflected 1 dimension of guideline-concordant care: namely, continuation of therapy for an extended period of time. We did not have information on adequacy of dosage. We did not examine medication switches or augmentations, 2 recommended strategies when patients fail to respond to initial treatment or have serious side effects,[3,4,29] because we were not able to determine the clinical validity of either. The clinical significance of missing a few days of antidepressant medication on a monthly basis is less clear than having a significant gap in treatment since some antidepressants have long half-lives. Thus, findings regarding monthly possession should be interpreted as secondary to those pertaining to disruption. We focused on generic (vs branded) initiation and did not consider subsequent switches between generic and branded antidepressants, which were infrequent. We also do not have information on prescribers or the benefit design of the Part D prescription drug plans.

CONCLUSIONS

Our study provides strong evidence supporting generic initiation to improve adherence to antidepressant therapy among Medicare patients. The benefits result from the lower out-of-pocket cost associated with generic antidepressants. These benefits were augmented while patients were experiencing the coverage gap under Part D. Our findings imply that generic prescribing, a strategy within easy reach of clinicians, can be an important tool to further improve adherence to antidepressant treatment and to mitigate negative effects of the Part D benefit structure. More broadly, to assist their patients in making healthcare more affordable, clinicians should consider the economic impact of their treatment decisions, raise the issue of ability to pay with patients, and discuss options. States that do not currently mandate generic substitution (unless with a "dispense as written" request by the prescriber or patient) or that require patient consent for generic substitution may consider more restrictive policies to further reap the benefits of generic use.

Author Affiliations: From Department of Public Health, Weill Cornell Medical College (YB, AMR, HS), New York, NY; Department of Psychiatry, College of Physicians and Surgeons, Columbia University (HAP), New York, NY; NewYork-Presbyterian Hospital (HAP), New York, NY; University of Pittsburgh, School of Public Health (JMD), Pittsburgh, PA.

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Address correspondence to: Yuhua Bao, PhD, 402 E 67th St, New York, NY 10065. E-mail: yub2003@med.cornell.edu.

REFERENCES

1. Stagnitti MN. *The Top Five Therapeutic Classes of Outpatient Prescription Drugs Ranked by Total Expense for Adults Age 18 and Older in the U.S. Civilian Noninstitutionalized Population, 2004.* Rockville, MD: Agency for Healthcare Research and Quality; 2006.

2. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry.* 2009;66(8):848-856.

3. Depression Guideline Panel. *Treatment of Major Depression.* US Department of Health and Human Services, eds. Rockville, MD: Agency for Health Care Policy and Research; 1993; *Depression in Primary Care;* vol 2.

4. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder.* 3rd ed. Arlington, VA: American Psychiatric Association; 2010.

5. The State of Health Care Quality: Reform, the Quality Agenda and Resource Use. Washington, DC: National Committee for Quality Assurance; 2010.

6. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. *JAMA.* 2007;298(1):61-69.

7. Zivin K, Madden JM, Graves AJ, Zhang F, Soumerai SB. Cost-related medication nonadherence among beneficiaries with depression following Medicare Part D. *Am J Geriatr Psychiatry.* 2009;17(12): 1068-1076.

8. Ventimiglia J, Kalali AH. Generic penetration in the retail antidepressant market. *Psychiatry (Edgmont).* 2010;7(6):9-11.

9. Shrank WH, Hoang T, Ettner SL, et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. *Arch Intern Med.* 2006;166(3): 332-337.

10. Hoadley J, Summer L, Hargrave E, Cubanski J, Neuman T. *Analysis of Medicare Prescription Drug Plans in 2011 and Key Trends since 2006.* Kaiser Family Foundation. http://www.kff.org/medicare/upload/8237.pdf. Published September 29, 2011. Accessed September 15, 2012.

11. Hellerstein JK. The importance of the physician in the generic versus trade-name prescription decision. *Rand J Econ.* 1998;29(1):108-136.

12. Shrank WH, Choudhry NK, Agnew-Blais J, et al. State generic substitution laws can lower drug outlays under Medicaid. *Health Aff (Millwood).* 2010;29(7):1383-1390.

13. Medicare Fact Sheet. Medicare Prescription Drug Benefit. Menlo Park, CA: Kaiser Family Foundation; 2009. Publication 7044-10.

14. BUCCANEER Computer Systems & Service, Inc. Chronic Condition Data Warehouse: Medicare Administrative User Guide: Version 1.8. http://www.ccwdata.org/cs/groups/public/documents/document/ccw_userguide.pdf. Published 2011. Accessed March 26, 2012.

15. Zhang Y, Baik SH, Zhou L, Reynolds CF, Lave JR. Effects of Medicare Part D coverage gap on medication and medical treatment among elderly beneficiaries with depression. *Arch Gen Psychiatry.* 2012;69(7): 672-679.

16. Medicare Fact Sheet. Low-Income Assistance Under the Medicare Drug Benefit. Menlo Park, CA: Kaiser Family Foundation; 2009. Publication 7327-05.

17. Cerner Multum Inc. Lexicon Plus. http://www.multum.com/Lexicon.html. Accessed September 16, 2011.

18. Lebowitz BD, Pearson JL, Schneider LS, et al. Diagnosis and treatment of depression in late life: consensus statement update. *JAMA.* 1997;278(14):1186-1190.

19. National Committee for Quality Assurance. Proposed Changes to Existing Measure for HEDIS®1 2009: Antidepressant Medication Management (AMM). Washington, DC: National Committee for Quality Assurance; 2008.

20. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81(3):515-526.

21. BUCCANEER Computer Systems & Service, Inc. CMS Chronic Condition Data Warehouse Condition Categories. http://www.ccwdata.org/cs/groups/public/documents/document/ccw_conditioncategories.pdf. Published October 2010. Accessed December 26, 2012.

22. Vlahiotis A, Devine ST, Eichholz J, Kautzner A. Discontinuation rates and health care costs in adult patients starting generic versus brand SSRI or SNRI antidepressants in commercial health plans. *J Manag Care Pharm.* 2011;17(2):123-132.

23. Harding KJ, Rush AJ, Arbuckle M, Trivedi MH, Pincus HA. Measurement-based care in psychiatric practice: a policy framework for implementation. *J Clin Psychiatry.* 2011;72(8):1136-1143.

24. Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review. Rockville, MD: Agency for Healthcare Research and Quality; 2011.

25. Simon GE, Perlis RH. Personalized medicine for depression: can we match patients with treatments? *Am J Psychiatry.* 2010;167(12): 1445-1455.

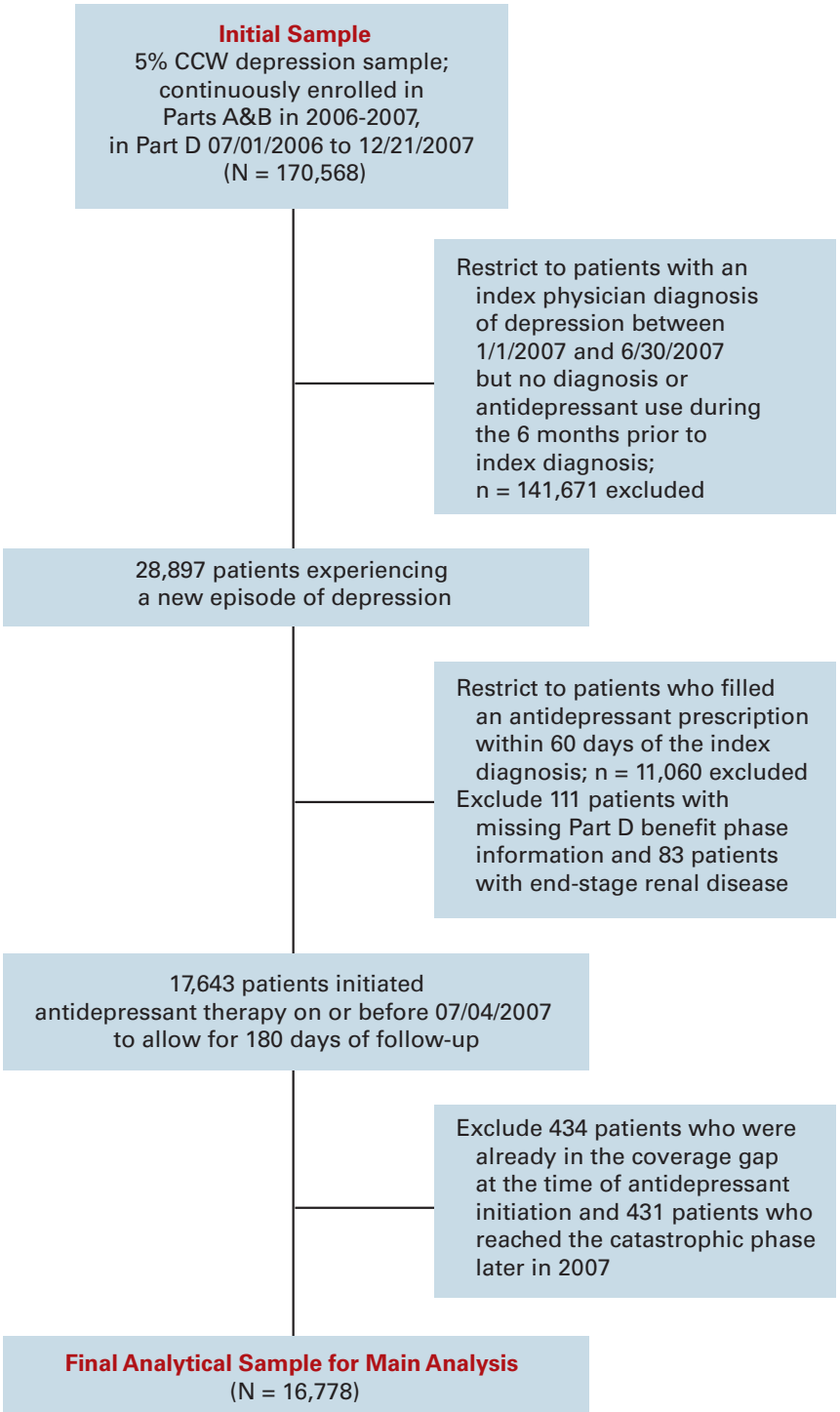
26. Frank RG, Zeckhauser RJ. Custom-made versus ready-to-wear treatments: behavioral propensities in physicians' choices. *J Health Econ.* 2007;26(6):1101-1127.

27. Donohue JM, Morden NE, Gellad WF, et al. Sources of regional variation in Medicare Part D drug spending. *N Engl J Med.* 2012;366(6): 530-538.

28. Heikkilä R, Mäntyselkä P, Ahonen R. Price, familiarity, and availability determine the choice of drug—a population-based survey five years after generic substitution was introduced in Finland. *BMC Clin Pharmacol.* 2011;11(1):20.

29. Schulberg HC, Katon W, Simon GE, Rush AJ. Treating major depression in primary care practice: an update of the Agency for Health Care Policy and Research Practice Guidelines. *Arch Gen Psychiatry.*1998; 55(12):1121-1127. ■

■ **eAppendix.** Generic Initiation of and Adherence to Antidepressant Therapy Under Medicare Part D: Development of the Study Cohort for Main Analysis and Sample Sizes



CCW indicates Medicare Chronic Condition Data Warehouse.