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Antidepressant Reformulations: Who Uses Them and What Are the Benefits?

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Abstract

The Hatch-Waxman Act provides pharmaceutical manufacturers an incentive to introduce reformulations of existing products about to lose patent protection in order to extend marketing exclusivity and maintain high prices. Antidepressant reformulations are particularly common. To determine whether antidepressant reformulation use confers benefits, we examine who uses reformulations, and compare medication continuation and the likelihood of receiving guideline-consistent pharmacotherapy duration among reformulation and original formulation users. We find some evidence of benefit for subgroups of antidepressant users, although benefits vary across reformulations.

With generic entry reducing market share for top-selling brand drugs in a number of classes, many pharmaceutical manufacturers are reformulating their existing products in an attempt to extend the life cycle of these drugs.¹ Under the Hatch-Waxman Act of 1984, manufacturers can obtain three to five additional years of market exclusivity for a reformulation.² Consequently, manufacturers have an incentive to shift demand for an original formulation that will soon lose patent protection to a reformulation of the same drug.³

Critics of the pharmaceutical industry assert that manufacturers devote too many resources to developing products like “me-too” drugs and reformulations that are only marginally different from existing products, and thus of limited value to society, rather than to developing breakthrough drugs.⁴ In contrast, others argue that reformulations represent advances in safety or efficacy and result in increased patient compliance.⁵

Reformulations are particularly common among psychiatric medications. These reformulations often involve less frequent dosing, more controlled release (i.e., the active ingredient is released more gradually during the day), or easier-to-administer dosing (e.g., a tablet that dissolves on the tongue) than the originator products. In theory, reformulations could be particularly useful for some patients with mental illness, such as patients for whom the illness itself limits their ability to adhere to a medication regimen or patients who experience intolerable side effects from existing medications. However, little is known about the benefits of reformulations as they are used in real-world settings.

To determine if benefits exist, we examined use of several antidepressant reformulations among Florida Medicaid enrollees. Specifically, we identified characteristics of reformulation users, examined whether reformulation users with major depression are more likely to receive guideline-consistent antidepressant duration than original formulation users, and examined whether reformulation users continue taking antidepressants longer than original formulation users.

Antidepressant Reformulations

We studied six reformulated antidepressants: two selective serotonin reuptake inhibitors (SSRIs) (Paxil CR and Lexapro), and four others (Effexor XR, Remeron Soltab, Wellbutrin SR, and Wellbutrin XL). Four are extended-/controlled-release formulations (Effexor XR, Paxil CR, Wellbutrin SR, and Wellbutrin XL). This type of reformulation would not be expected to have different biologic activity than its original formulation, but could have reduced side effects or, in some cases, require less frequent dosing.⁶ Remeron Soltab is a dissolvable tablet targeted at patients who have difficulty swallowing. Although potentially easier to administer than standard tablets, Remeron Soltab would not be expected to have different biologic properties or side effects than Remeron once ingested. Lexapro is a different type of reformulation. Celexa is a mixture of two mirror-image molecules (isomers) - one that contributes to its antidepressant effect and one that doesn't. In creating Lexapro, the manufacturer removed the molecule that doesn't contribute to Celexa's antidepressant effect, leaving only the molecule that does. This single-isomer drug could, in theory, be more potent or faster-acting, so one may find larger differences in either efficacy or tolerance between Lexapro and Celexa than between the other reformulations and their original forms.⁷

Although the manufacturers' marginal costs of producing reformulations are likely similar to the marginal production costs for the original formulations, prices paid by payers are often considerably higher for reformulations than for generic versions of the original products. For example, online drugstore.com shoppers paid \$106.99 for a 30-day supply of the minimally-therapeutic dose of Paxil CR versus \$13.99 for a similar dose of generic paroxetine as of January 2009.⁸

Clinical trial evidence on whether reformulations have greater efficacy or tolerability than the original formulations is relatively sparse and mixed at best.⁹ Among the six reformulations we assessed, even the most studied (Lexapro) has only a handful of trials comparing it to Celexa. Most studies for the six reformulations show little or no difference in efficacy. For those that do (a subset of the studies of Lexapro vs. Celexa; no studies of the other reformulations find efficacy differences), the difference in symptom reduction typically is relatively small, and some have argued not clinically meaningful.¹⁰ Results on tolerability differences are also mixed. Some studies show no difference, while a small number find that a particular reformulation may be associated with somewhat less severe side effects than its original formulation, particularly in the early phases of treatment. In theory, greater tolerability early in treatment could increase the likelihood that some patients continue taking the medication until they reach therapeutic durations, although these studies did not document differences in dropout rates due to side effects. Regardless of whether reformulations show greater efficacy or tolerability in carefully-selected populations enrolled in clinical trials, understanding whether there are any benefits from reformulation use requires measuring benefits for all users, not just clinical trial participants.

Methods

Using eligibility and claims data over the period July 1996 through June 2005, we first identified characteristics associated with use of a specific reformulation.¹¹ Then, we quantified

patient benefit in two ways. Our primary measure was the likelihood of receiving antidepressant therapy for a duration consistent with professional guidelines for acute phase treatment of major depression.¹² Receipt of such care has been documented to be predictive of significant improvement in mental health outcomes.¹³ To determine whether reformulation users are more likely to get appropriate pharmacotherapy, we compared the likelihood of receiving guideline-consistent duration among individuals using a given reformulation and individuals using its original formulation. We also examined an intermediate measure of benefit - medication continuation. Professional guidelines for mental health conditions other than major depression are not specific about appropriate antidepressant duration. However, the clinical literature suggests that there can be delays of several weeks or longer for an antidepressant to reach its maximum therapeutic effect, and antidepressant continuation up to some minimal duration is generally viewed as associated with positive outcomes like symptom reduction.¹⁴ Thus, we compared time to discontinuation among individuals using a given reformulation and individuals using its original formulation. If reformulations have greater tolerability, efficacy, or quicker onset of therapeutic benefit, then discontinuation rates should be lower.

We excluded individuals who were under age 18 and individuals for whom we were unable to observe all pharmacy and medical data (e.g., HMO enrollees, Qualified Medicare Beneficiaries). Additional detail on each of the three analyses is available in an Appendix.

Who Uses Reformulations?

To identify characteristics of reformulation users, we estimated a set of logit models (one for each reformulation) of the probability of filling a prescription for a given product in the year after its introduction among “current” antidepressant users, defined as those who filled any antidepressant prescriptions in the 90 days before the reformulation’s introduction.¹⁵

The models included the following covariates: age and age-squared; sex; race/ethnicity (black, Hispanic, white, other); eligibility category (Supplemental Security Income (SSI), Aid to Families with Dependent Children (AFDC), dual eligible, other); mental health/substance abuse (MH/SA) diagnoses in the six months before the observational window (anxiety but no depression, depression but no anxiety, both depression and anxiety, bipolar disorder, schizophrenia, other MH diagnoses, no MH diagnosis, SA disorder); presence of a diagnosis associated with difficulty swallowing; outpatient encounter with a psychiatrist during the past six months; use of inpatient MH/SA care in the past six months; nursing home residence during the observational period; number of months enrolled after reformulation introduction; and whether the patient had been taking the original formulation (e.g., equals “1” in Paxil CR model if the patient had been taking Paxil).

Guideline-consistent Antidepressant Duration for Major Depression

As our measure of guideline-consistent duration, we used the HEDIS measure for acute phase antidepressant management for major depression.¹⁶ According to this measure, an individual with a new episode of major depression (i.e., no recent depression diagnoses or antidepressants) who receives an antidepressant should remain on the medication throughout the acute phase of treatment (approximately first 12 weeks). To allow for delays in filling prescriptions, we considered individuals who received at least 84 days of medication in the first 114 days after the episode began to have met the guideline duration.

To compare the likelihood of receiving guideline-consistent duration among reformulation users and original formulation users, we created matched pairs of similar individuals using propensity score matching.¹⁷ We first identified individuals who initiated an episode of major depression in the two-year period after a reformulation was introduced and who used that reformulation. We then matched them to two other groups: 1) individuals with a new episode

of major depression during the same period who used the original formulation (“contemporaneous” original formulation users); and 2) individuals with a new episode of major depression just *before* the reformulation was introduced who used the original formulation (“non-contemporaneous” users of the original).¹⁸ We created the non-contemporaneous comparison group to address possible selection effects. For example, when both Celexa and Lexapro are available, there may be unobservable differences between individuals who take Lexapro and individuals who take Celexa. Therefore, we also compared Lexapro users to Celexa users in the period before patients had a choice between the two products.

The propensity score models controlled for the covariates from the logit models described above, as well as region, number of other medication classes used in the previous year (≤ 4 , 5-8, ≥ 9), and any cognitive deficit diagnosis in the previous six months.¹⁹ Using the matched pairs, we estimated a logit model for the probability of receiving guideline-consistent duration for each comparison (e.g., Paxil CR users and non-contemporaneous Paxil users). Because Wellbutrin SR, Effexor XR, and Wellbutrin XL were introduced either at the very beginning or end of our study period, we could not study these products due to an insufficient observational period. We were unable to study Remeron Soltab because the number of Remeron Soltab and Remeron users with a new episode of major depression was too small.

Time to Discontinuation

To compare time to antidepressant discontinuation among reformulations users and original formulations users, we created a second set of propensity score matches. All new antidepressant users (i.e., those who hadn’t filled any antidepressant prescriptions in the previous 90 days), regardless of diagnosis, were eligible for matching. Using the matched pairs, we estimated Kaplan-Meier curves of time to discontinuation.

Results

Over the ten-year study period, characteristics of antidepressant users remained relatively stable (Exhibit 1). Approximately 40% were over age 65. Most were white (58-62%), while 12% were black and 6-10% were Hispanic. Almost half were dually-eligible for Medicare. Over two-thirds (69%-72%) had no MH diagnosis in the past six months and most (77%-83%) had not seen a psychiatrist during the past six months.

Who Uses Reformulations?

Reformulation use was generally less common among younger enrollees, men, blacks (relative to whites), and SSI beneficiaries (relative to dual eligibles) (Exhibit 2). Original formulation users were more likely to fill a prescription for the reformulation once it was available than people who had been using a different drug.

Individuals who had seen a psychiatrist were more likely to receive a reformulation. Patients diagnosed with both anxiety and depression were more likely to get an SSRI reformulation but not more likely to get another reformulation.²⁰ Individuals with no recorded MH diagnosis, generally more common among patients treated in primary care than in the specialty MH sector, were less likely to receive four of the reformulations (no significant difference for the other two). Patients with recent MH/SA inpatient use were more likely to get two of the reformulations (no significant difference for the others). Individuals likely to have difficulty swallowing were more likely to use Remeron Soltab but not more likely to use the others (all pills that must be swallowed).

Guideline-consistent Antidepressant Duration for Major Depression

In both the non-contemporaneous and contemporaneous comparisons, Lexapro and Paxil CR patients with major depression were more likely to receive guideline-consistent duration than similar patients using the original formulation (Exhibit 3). For example, 46% of Lexapro users versus 36% of non-contemporaneous Celexa users received guideline-consistent duration. The differences were significant for all comparisons except Paxil CR/non-contemporaneous Paxil, which was of borderline significance.

Time to Discontinuation

Celexa users were more likely to discontinue earlier than Lexapro users (Exhibit 4). Median days to discontinuation was 91 for Lexapro users vs. 64 for Celexa users in the non-contemporaneous comparison, and 76 vs. 61 in the contemporaneous comparison. The curves diverged around thirty days after medication initiation, suggesting that Lexapro users were more likely to refill their initial prescription than Celexa users.

For Paxil CR vs. Paxil, there was a statistically-significant, although smaller, difference in time to discontinuation. For example, median days to discontinuation was 64 for Paxil CR users vs. 61 for non-contemporaneous Paxil users. Again, the curves diverged around thirty days after initiation. For Remeron Soltab vs. Remeron, there was no statistically-significant difference for the non-contemporaneous comparison and only a very small significant difference for the contemporaneous comparison.

Conclusions

Using duration-based measures, we found some evidence of benefit associated with reformulation use, although our findings suggest that all reformulations are not created equal. Lexapro users, on average, continued longer than Celexa users, and Paxil CR users continued longer than Paxil users. The difference was larger for Lexapro vs. Celexa, which might be expected since Lexapro is more different from Celexa than Paxil CR is from Paxil. There was no notable difference for Remeron Soltab vs. Remeron. However, given that a dissolvable tablet's primary potential benefit may be ease of administration as opposed to reduced side effects or improved efficacy, this result may not be surprising.

Reformulation benefits may be unequal across subgroups of antidepressant users. Given the relative clarity of the major depression treatment guidelines on appropriate duration of pharmacotherapy, our findings that Lexapro and Paxil CR users with major depression were more likely to receive guideline-consistent antidepressant duration compared to similar users of the original formulations suggest positive benefit associated with reformulation use for this population. The implications of our results on time to discontinuation for the entire population of reformulation users (not just those with major depression) are less clear, however. Longer use may not be better for all patients, and the indications for antidepressant use are unclear for the approximately two-thirds of users with no recorded MH diagnosis in the previous six months. Some may be individuals with episodic major depression; others may be receiving the reformulation for depression or anxiety symptoms but no clear diagnosis, or even for chronic pain.

Given that we could only document clear benefits for individuals with a diagnosis of major depression (88-91% of antidepressant users in our population), should we expect all reformulation users to derive equal benefit? One could argue that reformulation users are revealing their preference for the reformulation by their willingness to pay the additional costs associated with its use. However, Medicaid recipients typically pay either a nominal or no copayment for each prescription filled and often face either no differential cost or only a very

small one if they select a reformulation over its original formulation, so their choice of a reformulation does not involve weighing the full costs and benefits.²¹ Also, some patients and their physicians may be influenced by manufacturer promotional efforts to select a reformulation even though the expected benefits may not be greater for the patient.

It is also possible that physicians may be doing a careful job of matching reformulations to those patients likely to get greater benefit from them, and thus some potential users would not derive the benefits we documented. We found that patients with difficulty swallowing were more likely to get Remeron Soltab but not the reformulations that must be swallowed. Patients with comorbid depression and anxiety, and thus perhaps more complicated courses of illness, were more likely to use an SSRI reformulation. Reformulation use was more common among patients who recently saw a psychiatrist or were hospitalized, who also may be more likely to have relatively severe or complicated conditions, although it is also possible that psychiatrists are more likely to prescribe new medications or are subject to a greater level of manufacturer promotion. While our results may be somewhat suggestive of some level of matching, we are unable to determine the extent to which good matches are being made as opposed to inefficient matches.

Alternatively, it is also possible that doctors who prescribe reformulations are “better” doctors who may be more successful at convincing their patients to continue an antidepressant until guideline-consistent durations are reached. Our models control for whether the enrollee is being treated by a psychiatrist, but our data do not allow us to distinguish effects of the individual provider or other provider-level characteristics.

Given that we found some evidence of benefit, at least for patients with major depression, how might these benefits compare to the costs of the medications from a societal perspective? Is their value sufficient to warrant their development? According to economic theory, long-run societal marginal costs for reformulations approximate their marginal costs of production (i.e., the manufacturing costs).²² In most cases, a reformulation’s marginal production costs are likely to be similar to those for the original formulation (e.g., the marginal costs of producing one tablet of Paxil are probably similar to the marginal costs of producing one tablet of Paxil CR). The additional R&D costs likely depend on the novelty of the reformulation, although in most cases R&D costs should be lower than for developing an entirely new drug. Also, testing requirements are typically less extensive for reformulations than for new molecules.²³

If the societal marginal costs are in fact relatively low, a reformulation that could show even very limited benefits would add value from a societal perspective. If so, the Hatch-Waxman Act provisions governing reformulations may introduce inefficiencies into the market. The law provides incentives for firms to delay reformulation introduction until patent expiration approaches for the original formulation in order to take maximum advantage of the exclusivity extension.²⁴ As a result, release of reformulations for which there is some value is delayed from society’s perspective, and policymakers may wish to reconsider the Hatch-Waxman provisions governing reformulations.

From a payer’s perspective, the value associated with reformulations is less clear. If the government (acting as a payer for Medicare and Medicaid) compared the incremental costs and benefits of reformulations relative to original formulations or other similar drugs (for example, as NICE might do in the UK), it is unclear whether the magnitude of benefits we documented would be sufficient to warrant a decision to cover the reformulation given the current differences in prices that payers typically face. Manufacturers might be willing to negotiate lower prices if the drug might not be covered (as they have done in some cases in the UK) or the government could attempt to target reformulations to those with higher marginal benefits (e.g., Soltab only for those with documented difficulty swallowing) using tools like

prior authorization. For employers, coverage of reformulations will depend in part on the labor market and the offerings of similar employers. Payers might also be more willing to cover reformulations if their use offset other health care expenditures, although there is no such evidence to date on offsets.

Several limitations should be noted. First, using claims data to understand medication utilization allows one to study use in a large population treated in real-world settings; however, clinical information is somewhat limited, and MH diagnoses can be undercoded. Claims data do not capture medications not reimbursed by Medicaid, such as free samples. Second, propensity score matching only addresses differences in observable characteristics. There may be unmeasured characteristics that influence selection of one drug or another. Our approach of comparing reformulation users with both contemporaneous and non-contemporaneous users of original formulations helps to address this potential selection, but may not resolve it entirely. Third, we focus on two measures of benefit that are typically associated with improved mental health outcomes. We are unable to capture all potential benefits that could result, such as increased labor market productivity or ease of administration. Fourth, we use data from a single state Medicaid program. Utilization patterns for reformulations may differ in privately-insured or non-dual-eligible Medicare populations.

Our results provide some evidence of benefit for reformulations, although the benefit varies across reformulations and may differ by diagnosis. We also documented racial disparities in receipt of reformulated antidepressants, as blacks were significantly less likely to receive reformulations than whites.²⁵ The fact that some of these medications confer benefits for at least certain subpopulations makes these disparities troubling and highlights the need for research to understand the factors driving them.

References

1. Pharmaceutical Business Review Online. Pharma Turns to Reformulation to Maximize ROI. Dec 82006 [October 9, 2008]. Available at http://www.pharmaceutical-business-review.com/article_feature.asp?guid=877C0956-1BF3-4982-986F-805E7DCD60C9
2. The original product's patent is not extended. Additional exclusivity applies only to the reformulation. Most types of reformulations (e.g., controlled-release forms) would receive three years of exclusivity. Lexapro, marketed as a new chemical entity, received five.
3. Huskamp HA, Donohue JM, Koss C, Berndt ER, Frank RG. Generic Entry, Reformulations and Promotion of SSRIs in the U.S. *Pharmacoeconomics* 2008;26(7):603–616. [PubMed: 18563951]
4. E.g., Angell M. *The Truth about Drug Companies: How They Deceive Us and What to Do about It*. New York:Random House;2004
5. Wertheimer, AI.; Santella, TM. Pharmaco-evolution: the Advantages of Incremental Innovation. [October 2, 2008]. available at: <http://www.who.int/intellectualproperty/submissions/Pharmaco-evolution.pdf>
6. A review (across medication classes) of compliance studies that used electronic monitoring found that number of doses per day is inversely related to compliance Claxton AJ, Cramer J, Pierce C. A Systematic Review of the Associations between Dose Regimens and Medication Compliance. *Clinical Therapeutics* 23(8)2001::1296–1310.1310 [PubMed: 11558866]
7. Lexapro, The Single-Isomer of Celexa, Receives FDA Approvable Letter. [January 21, 2009]. available at <http://www.frx.com/news/PressRelease.aspx?ID=250711>
8. www.drugstore.com on January 22, 2009
9. See Appendix for a complete list of studies described in this paragraph.
10. E.g., Svensson S, Mansfield PR. Escitalopram: Superior to Citalopram or a Chiral Chimera? *Psychotherapy and Psychosomatics* 732004::10–16.16 [PubMed: 14665791]
11. The only antidepressant prior authorization requirement during the ten-year period was implemented in 2/05 (for Celexa). The observation window for our two main analyses ends before 2/05.

12. E.g., Agency for Health Care Policy and Research (AHCPR). Depression in Primary Care: Volume 2. Treatment of Major Depression. Rockville, MD U.S. Department of Health and Human Services 1993
13. Rost K, Dickinson LM, Fortney J, Westfall J, Hermann RC. Clinical Improvement Associated with Conformance to HEDIS-based Depression Care. *Mental Health Services Research* 2005;7(2):1–14. [PubMed: 15832689]
14. AHCPR. Treatment of Major Depression.
15. We estimated similar models of the probability of reformulation use among new antidepressant users. Results were similar, so we do not present results for incident users.
16. National Committee for Quality Assurance. HEDIS 2008 Summary Table of Measures, Product Lines and Changes. [October 14, 2008]. Available at: http://www.ncqa.org/Portals/0/HEDISQM/HEDIS2008/2008_Measures.pdf
17. D'Agostino RB Jr. Propensity Score Methods for Bias Reduction in the Comparison of a Treatment to a Non-randomized Control Group. *Statistics in Medicine* 1998;17(19):2265–2281. [PubMed: 9802183]
18. We performed a 1-1 matched analysis without replacement on the basis of the estimated propensity score of each patient. Additional detail provided in Appendix.
19. Depression diagnosis variables were excluded, since all were diagnosed with major depression.
20. Most SSRIs have indications for treating both anxiety and depression, while most other antidepressants do not.
21. Crowley, JS.; Ashner, D.; Elam, L. State Medicaid Outpatient Prescription Drug Policies: Findings from a National Survey. [October 29, 2008]. Available at: <http://www.kff.org/medicaid/upload/State-Medicaid-Outpatient-Prescription-Drug-Policies-Findings-from-a-National-Survey-2005-Update-report.pdf>
22. Frank RG, et al. New Analyses of Costs and Effectiveness in CATIE. working paper
23. Reformulation manufacturers must demonstrate bioequivalence and safety.
24. In deciding when to introduce, manufacturers balance time needed to shift demand onto the reformulation against the limited exclusivity period. See Kina S. Optimal Regulation of Pharmaceutical Line Extensions. working paper.
25. A similar result was found in Lleras-Muney A, Lichtenberg FR. The Effect of Education on Medical Technology Adoption: Are the More Educated More Likely to Use New Drugs? NBER Working Paper 9185. Available at: <http://www.nber.org/papers/w9185>. [January 13 2009];

Exhibit 1

Characteristics of Antidepressant Users, 1997-2004

Characteristics	1997	2001	2004
Number of Users	115,683	161,260	203,274
Female	73%	72%	73%
Race			
White	62%	60%	58%
Black	12%	12%	12%
Hispanic	6%	8%	10%
Other	20%	20%	20%
Age			
18-25	3%	4%	4%
26-35	11%	10%	10%
36-45	17%	17%	15%
46-55	13%	16%	16%
56-64	13%	14%	15%
65+	43%	40%	40%
Eligibility Status			
AFDC	8%	8%	8%
SSI	25%	24%	22%
Dual	48%	46%	45%
Other	18%	22%	25%
Mental Health Dx			
Depression – all	20%	19%	17%
Major depression	12%	11%	9%
Anxiety	5%	6%	6%
Depression + Anxiety	2%	2%	2%
No Mental Health Dx	69%	70%	72%
Substance Use	4%	4%	3%
Difficulty Swallowing	5%	5%	5%
Nursing Home Resident	10%	11%	11%
Seen Psychiatrist	23%	21%	17%
MHSA Inpatient Use	3%	3%	2%
# Other Medication Classes			
≤4	39%	33%	30%
5-8	37%	36%	33%
>8	23%	31%	37%

Note: The number of other medication classes refers to the number of medication classes used besides antidepressants.

Exhibit 2
 Characteristics of Current Antidepressant Users Who Fill a Prescription for a Reformulation

Characteristic	SSRIs		Other Antidepressants				
	Lexapro (n=8824)	Paxil CR (n=6322)	Remeron Softab (n=2437)	Effexor XR (n=1246)	Wellbutrin SR (n=997)	Wellbutrin XL (n=6636)	
Age	+	+	NS	+	+	+	
Age Squared	-	-	+	-	-	-	
Male	-	-	NS	-	NS	-	
Black (vs. White)	-	-	-	-	-	-	
Hispanic (vs. White)	+	+	+	NS	NS	+	
SSI (vs. Dual Eligible)	-	-	NS	-	-	-	
AFDC (vs. Dual Eligible)	-	NS	NS	-	NS	NS	
Anxiety (vs. Depression, no Anxiety)	NS	+	NS	-	NS	-	
Anxiety + Depression (vs. Depression, no Anxiety)	+	+	NS	NS	NS	NS	
No Mental Health Dx	-	-	NS	-	NS	-	
Inpatient MH/SA Use	+	NS	NS	NS	+	NS	
Seen Psychiatrist	+	+	+	+	+	+	
Nursing Home Resident	+	-	+	NS	NS	-	
Use of Original Formulation	+	+	+	+	+	+	
Difficulty Swallowing	NS	NS	+	NS	NS	NS	

Notes: This exhibit summarizes results from the drug-specific logit models examining characteristics of reformulation users, among those who were currently using another antidepressant at the time a given reformulation was introduced. These models predict the likelihood that a current antidepressant user will fill a prescription for the reformulation in the first year after the reformulation comes on the market. "NS" = not statistically significant (p≥0.05); "+" = more likely to receive a reformulation; "-" = less likely to receive a reformulation. The number of individuals using each reformulation within a year after its introduction is provided in parentheses below the drug name.

Exhibit 3
Likelihood of Receiving Appropriate Pharmacotherapy Duration for Major Depression

Cohort	Appropriate Duration %	Number of Matched Pairs	% Appropriate Duration [Reformulation – Comparison] (95% CI)
Non-contemporaneous Matched Samples			
Lexapro (Reformulation)	45.5	541	9.4 (3.8, 15.1)
Celexa	36.6		
Paxil CR (Reformulation)	37.0	692	4.0 (-0.1, 8.9)
Paxil	33.0		
Contemporaneous Matched Samples			
Lexapro (Reformulation)	42.8	173	11.0 (0.5, 21.5)
Celexa	31.8		
Paxil CR (Reformulation)	42.0	262	14.9 (6.5, 23.3)
Paxil	27.1		

Notes: These are the results from the logit models of likelihood of receiving guideline-level pharmacotherapy duration among individuals with a new episode of major depression.

Exhibit 4
Results from Kaplan-Meier Analysis of Time to Antidepressant Discontinuation

Cohort	Median Days to Discontinuation	Relative Risk [Comparison to Reformulation]	95% Confidence Interval	# of Matched Pairs
Non-contemporaneous Matched Samples				
Lexapro	91	0.83	(0.80, 0.85)	18,045
Celexa	64			
Paxil CR	64	0.87	(0.85, 0.89)	23,713
Paxil	61			
Remeron Soltab	65	1.04	(1.00, 1.08)	10,820
Remeron	66			
Contemporaneous Matched Samples				
Lexapro	76	0.84	(0.80, 0.87)	7,985
Celexa	61			
Paxil CR	63	0.88	(0.85, 0.91)	14,307
Paxil	61			
Remeron Soltab	63	0.94	(0.90, 0.98)	9,888
Remeron	61			

Note: Kaplan-Meier plots are presented the Appendix.