# Antidepressant Nonadherence in Routine Clinical Settings Determined From Discarded Blood Samples

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## ABSTRACT

***Objective:*** Antidepressant nonadherence is common and represents a potentially modifiable risk factor for treatment nonresponse. We used a novel approach based on discarded blood samples from routine clinical blood draws to assess treatment nonadherence in a general clinical population.

***Method:*** Individuals diagnosed with or without major depressive disorder (using *ICD-9)* and prescribed sertraline, citalopram, bupropion, or venlafaxine in January 2014 were identified by querying the electronic health record of 2 academic medical centers. Discarded blood samples from routine blood draws for 109 individuals within 14–90 days of treatment initiation were anonymized and then assessed for detectable serum antidepressant levels.

***Results:*** Overall, 17% of samples lacked detectable levels of the index antidepressant. Individuals with public versus private insurance were more likely to have undetectable antidepressant levels ($\chi^2_1 = 5.07$, $P = .02$) as were those receiving shorter-term (< 90 days) prescriptions ($\chi^2_1 = 4.03$, $P = .05$).

***Conclusions:*** In general, electronic prescribing data provided a reasonable proxy for actual antidepressant use. Additionally, up to 1 in 5 individuals prescribed an antidepressant may not be adherent, suggesting the need for further efforts to reduce treatment nonadherence.


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Most antidepressants are more efficacious when ingested on a consistent basis, and abundant data suggest nonadherence is associated with poorer treatment response. Nonadherence therefore represents a possible target for improving outcomes of antidepressant treatment. But how common is nonadherence? Published reports vary widely, from less than 25% to more than 50%.[1–3] This variation more likely has to do with context; for example, adherence may be greater in randomized, controlled trials with greater visit frequency and systematic assessment than in naturalistic studies.[1] Likewise, the means of establishing nonadherence leads to varied results; in particular, strategies for measuring adherence such as medication event monitoring system caps or scheduled blood levels more likely increase adherence. In clinical practice, 1 study[4] suggested clinicians either overestimate or underestimate adherence more than half the time.

Another approach to estimating adherence relies on electronic health records or claims data, with the assumption that patients only fill medications that they continue to use. The most common measure in claims data is medication possession ratio, the proportion of time in follow-up during which a patient possesses a given medication as inferred from prescription and refill data.[5,6] Given the widespread application of electronic health records for efficient pharmacovigilance and biomarkers studies, understanding the reliability of estimates of adherence is likely to gain importance.[7–10]

In an effort to directly measure adherence during standard clinical care, without requiring an intervention known to influence adherence, we utilized a system that allows routine blood samples drawn for any reason to be matched with clinical data and then anonymized. This strategy allowed us to examine the presence of detectable levels of a given antidepressant in individuals for whom the antidepressant was ordered via the electronic health record.

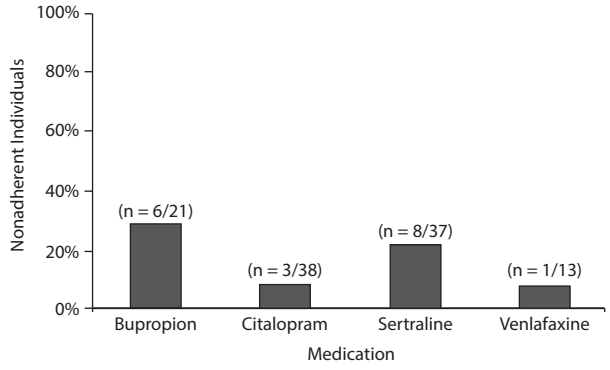
## METHOD

### Overview and Data Set Generation

We identified all individuals age 18 or older and electronically prescribed 1 of 4 antidepressants (citalopram, sertraline, venlafaxine, or bupropion) in January 2014 at 2 large academic medical centers, Massachusetts General Hospital and Brigham and Women's Hospital (BWH), in primary care or outpatient specialty clinics. In these centers, all prescribing is now required to be done electronically, with medications reconciled at each patient contact.

A data mart containing all sociodemographic and clinical data drawn from the electronic health record, including subject age, sex, self-reported race/ethnicity, insurance status at time of prescription, and prescriber status (psychiatry or non-psychiatry; specialist or primary care) was generated using i2b2 server software (i2b2 v1.6, Boston, Massachusetts),[11] a computational framework for managing human health data.[12,13] In this health system, Hispanic or Latino ethnicity is not captured separately from race, so Hispanic subjects are analyzed as a distinct group. Presence or absence of major depressive disorder or depressive disorder not otherwise

**Figure 1. Proportion of Individuals With Undetectable Serum Antidepressant Levels, by Medication**




specified was determined based on *ICD-9* code (296.2*, 296.3*, or 311.*) within 1 year prior to prescription; the latter code was included as it is commonly applied by primary care providers to correspond to a depressive episode in this health system. Age-adjusted Charlson comorbidity index, a validated measure of overall burden of medical illness, was also calculated per previous reports.[14]

The Crimson Biomaterials Collection Core Facility at BWH allows pre-specified, discarded blood samples to be flagged, matched with selected clinical data, and then anonymized. As such, the Institutional Review Board can waive the requirement for informed consent as detailed by 45 CFR 46.116 for research with discarded human materials. The Partners Institutional Review Board approved all aspects of this study. For this pilot investigation, we allowed sample collection to continue until 90 days had elapsed since prescription initiation. (Of note, because data are not accessioned to the i2b2 data mart in real time and additional time is required to extract eligible subjects and transfer the subject list to laboratory sites, a minimum of 14 days elapsed between active prescription and possibility of sample collection using Crimson). Patients whose providers discontinued their prescriptions or changed treatments in the electronic health record prior to sample collection were excluded from analysis.

Samples were transferred to the Analytical Psychopharmacology Laboratory at the Nathan S. Kline Institute for Psychiatric Research where they were analyzed for detectable antidepressant and metabolite levels via liquid chromatography, with the laboratory protocol modified as necessary for each antidepressant and metabolite.[15–18] Because of the possible lag in sample handling after collection, only presence/absence of medication or metabolite, rather than relative levels, were examined. The lower limit of quantitation was set at 10 ng/mL for venlafaxine; 5 ng/mL for bupropion and sertraline; and 2.5 ng/mL for citalopram.[15–18] We chose these 4 antidepressants because they have relatively short half-lives (fewer than 1.5 days), which provided us with greater sensitivity to nonadherence than would medications with longer half-lives, and because they encompass multiple mechanisms of action and indication.

**Clinical Points**

- Antidepressant nonadherence is common and represents a potentially modifiable risk factor for treatment nonresponse.
- The use of electronic health records in conjunction with discarded blood samples allows a novel approach to estimating rates of nonadherence among patients.
- Up to 1 in 5 patients electronically prescribed a given antidepressant exhibited some degree of nonadherence.

### Analysis

The primary aim of this study was to estimate the proportion of individuals with undetectable antidepressant levels despite an active, recent prescription for 1 of 4 antidepressants. In addition, for hypothesis-generating purposes, we examined the association of undetectable levels with pre-specified sociodemographic and clinical features using $\chi^2$ or Student *t* test. We also compared relative rates of apparent nonadherence between antidepressant types by $\chi^2$ test. In all cases, statistical significance was reported at a level of $\alpha = .05$.

All analyses utilized Stata 13.1 (Statacorp, College Station, Texas).

## RESULTS

In all, 1,762 patients were identified as being prescribed a study antidepressant in January 2014. Discarded clinical blood samples were collected on 109 patients within 90 days of active prescription. This sample of patients was slightly older and had greater medical comorbidity than the underlying population (Supplementary eTable 1 at PSYCHIATRIST.COM). The assessed cohort included 109 patients, divided among bupropion (21; 19%), citalopram (38; 35%), sertraline (37; 34%), and venlafaxine (13; 12%). A mean (SD) of 48 (14) days elapsed between prescription and blood sample. Across all antidepressants, 18 (17%) had undetectable levels. Figure 1 illustrates percentage of nonadherence by medication; no significant differences between groups were observed.

In univariate analyses contrasting adherent and nonadherent individuals (Table 1), age and sex were not significantly different between groups; those without private insurance were more likely to have undetectable levels ($\chi^2_1 = 5.07$, $P = .02$) as were those receiving shorter-term (< 90 days) prescriptions ($\chi^2_1 = 4.03$, $P = .05$). Individuals receiving prescriptions from nonpsychiatrists, those with lesser medical comorbidity, and those with continuing prescriptions or 2 or more refills on a prescription, were numerically but not statistically more likely to have undetectable levels.

## DISCUSSION

These results illustrate a novel means of characterizing antidepressant adherence among patients in naturalistic treatment settings, helping to bridge the gap between methods relying solely on claims data (ie, when prescriptions

**Table 1. Sociodemographic and Clinical Features of Individuals (N = 109) With and Without Detectable Serum Antidepressant Levels**

| | Detectable (n = 91) | | Undetectable (n = 18) | | Comparison | |
|---|---|---|---|---|---|---|
| Feature | % | n | % | n | $\chi^2_1$ | *P* value |
| Males | 40 | 36 | 28 | 5 | 0.89 | .35 |
| Public insurance | 33 | 30 | 61 | 11 | 5.07 | .02 |
| Psychiatric provider | 20 | 18 | 11 | 2 | 0.75 | .39 |
| Specialist | 57 | 52 | 44 | 8 | 0.98 | .32 |
| Depression diagnosis | 51 | 46 | 56 | 10 | 0.15 | .70 |
| Initial prescription | 16 | 15 | 28 | 5 | 1.28 | .26 |
| 2+ refills on prescription | 79 | 72 | 78 | 14 | 0.02 | .90 |
| 90-day or greater supply of prescription | 42 | 38 | 17 | 3 | 4.03 | .05 |
| Within 45 days following prescription (vs 45–90 days) | 42 | 38 | 50 | 9 | 0.42 | .52 |
| | Mean | SD | Mean | SD | Student *t* | *P* value |
| Age, y | 57.25 | 15.67 | 49.78 | 22.32 | 1.71 | .09 |
| Charlson comorbidity index | 7.42 | 5.71 | 5.61 | 5.57 | 1.23 | .22 |
| Days following prescription | 48.03 | 13.95 | 45.39 | 15.00 | 0.73 | .47 |

are filled), therapeutic drug monitoring conducted as part of clinical trials, and clinical practice. In general, nonadherence was somewhat less common than prior studies[2,3] might have suggested, with rates of 8%–29% depending on antidepressant. However, it is difficult to directly compare such rates, given the wide variety of methodologies employed.[1,2] In particular, an electronic-health-record–based methodology includes primary nonadherence (ie, prescriptions never filled) as well as discontinuation, in contrast with claims-based methods focused solely on the former.

In light of the modest sample size in this pilot investigation, it is not surprising that we did not identify marked differences between individuals with or without undetectable blood drug levels, with the exception of insurance type and prescription supply: those without private insurance were more likely to be nonadherent as were those receiving shorter-term (< 90 days) prescriptions. Notably, all of the antidepressants studied are, by design, available in generic form and are typically not restricted on payer formularies. Thus, the differences observed here are unlikely to reflect solely antidepressant cost. Consistent with a prior study[5] of antidepressant-treated patients with anxiety, we observed numerically but not statistically significantly greater adherence among patients whose medications were prescribed by a psychiatrist. Also consistent with a prior study[19] of antidepressant-treated patients with depression, we observed numerically poorer adherence among patients on their initial prescription. Finally, we note that the adherent group had higher Charlson comorbidity index scores (Table 1), suggesting that greater medical comorbidity is not likely to be a major determinant of nonadherence, at least in subjects with moderate levels of medical comorbidity.

All means of estimating nonadherence have substantial limitations, and this approach is no exception. Specifically, we were only able to sample individuals who had blood drawn as part of routine clinical care. This constraint might bias us toward individuals with greater medical comorbidity, which would make our results more relevant to general clinical populations with some degree of comorbidity (rather than younger, less-comorbid populations). However, we would expect that the majority of outpatient blood draws represent routine monitoring in primary care. In any case, it seems unlikely that patients would meaningfully change their medication adherence before blood is drawn unless it is intended for therapeutic drug monitoring.

A further limitation is the 14-day minimum lag between the prescription and blood sample, necessitated by the time required to generate and process a new clinical data set and to accession the sample list to participating laboratories. However, given that our adherence measure captures the prior 5–7 days (ie, ~5 half-lives) and that patients may not fill prescriptions for the first few days, measurement earlier than ~10 days would unlikely be informative. Here, we found that differences between individuals within the first 45 days, and the subsequent 45 days, were modest.

Another limitation is the possibility that some patients may discontinue treatment on the orders of the prescriber—for example, in the context of medication intolerance. When this occurs, clinicians in this health system are expected to formally discontinue medications in the electronic-prescribing system (ie, by entering the stop date for a given medication), as medication reconciliation occurs at each patient contact; therefore, those individuals were excluded from this analysis. Still, it is possible that undocumented discontinuation could inflate the apparent nonadherence reported here. In general, our prior work[20] suggests that it is unlikely that clinicians would document discontinuation in narrative notes without also updating the medication list.

Finally, this methodology allows only a snapshot of adherence at a particular point in time. While it is quite likely that patients with undetectable levels missed nearly all doses over the preceding week (in light of the half-lives of the antidepressant medications selected), we cannot distinguish degrees of nonadherence, and particularly so-called hidden nonadherence attributable to intermittent missed doses.[21] As such, our data answer a very focused but face-valid question: in a cohort of antidepressant-treated patients, what proportion has recently not been taking their medication?

Notwithstanding these limitations, this report adds to a body of evidence using diverse approaches that a subset of individuals prescribed antidepressant medications do not reliably take them. In this relatively small cohort, we did not find statistically significant differences between medications.

Our results are also relevant to efforts to use electronic health records for pharmacovigilance, comparative effectiveness, and other questions of substantial clinical importance where a randomized controlled trial is not feasible. They suggest that, while patients who are electronically prescribed a given antidepressant medication do not universally adhere to treatment, the majority do so on any given day. Still, in interpreting negative findings, the impact that nonadherence tends to bias results toward the null hypothesis must be considered. Our results may facilitate more precise modeling of the impact of nonadherence in pharmacovigilance studies.

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***Drug names:*** bupropion (Wellbutrin and others), citalopram (Celexa and others), sertraline (Zoloft and others).

***Potential conflicts of interest:*** **Dr Perlis** has served on scientific advisory boards for or received consulting fees from Genomind, Healthrageous, Pfizer, Perfect Health, Proteus Biomedical, Psybrain, and RID Ventures and receives royalties through Massachusetts General Hospital from Concordant Rater Systems (now UBC). Ms Roberson, Mr Castro, and Mr Cagan report no potential conflicts of interest.

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***Supplementary material:*** Available at PSYCHIATRIST.COM.

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# Supplementary Material

**Article Title:** Antidepressant Nonadherence in Routine Clinical Settings Determined From Discarded Blood Samples

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## List of Supplementary Material for the article



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**Supplementary eTable 1. Comparison of individuals with routine blood draws within 90 days of antidepressant prescription to those without.**

| | Prescribed study antidepressant in January 2014 (n = 1,762) | Antidepressant level assessed 14-90 days after prescription (n = 109) | Comparison | |
|---|---|---|---|---|
| Feature | % | % | $X^2 1$ | *P* value |
| Male sex | 29 | 38 | 3.56 | 0.17 |
| Public insurance | 30 | 38 | 2.28 | 0.13 |
| Psychiatric provider | 18 | 18 | 0.00 | 1.00 |
| Specialist (versus primary care) | 55 | 55 | 0.00 | 1.00 |
| MDD diagnosis* | 12 | 17 | 1.16 | 0.28 |
| Initial prescription | 19 | 18 | 0.00 | 1.00 |
| 2+ refills on prescription | 73 | 74 | 0.04 | 0.84 |

| | Mean | SD | Mean | SD | Student t | *P* value |
|---|---|---|---|---|---|---|
| Age (years) | 52.25 | 16.83 | 56.02 | 17.05 | 2.24 | 0.02 |
| Charlson comorbidity index | 4.30 | 4.29 | 7.12 | 5.71 | 5.06 | < 0.001 |

*MDD, major depressive disorder