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Pharmacokinetically and Clinician-Determined Adherence to an Antidepressant Regimen and Clinical Outcome in the TORDIA Trial

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Abstract

Objective—Nonadherence to antidepressant treatment may contribute to poor outcome and to suicidal adverse events in adolescent depression. We examine the relationship between adherence and both clinical response and suicidal events in participants in the Treatment of Resistant Depression in Adolescents (TORDIA) study.

Method—The relationship between adherence to medication and clinical outcome was assessed in 190 treatment-resistant depressed adolescents who were randomized to one of four cells: switch to another selective serotonin reuptake inhibitor (SSRI), switch to venlafaxine, or either of these two medication switches plus cognitive behavioral therapy. Plasma levels of antidepressant drug and metabolites were determined after 6 and 12 weeks of treatment. A twofold or greater variation in the dose-adjusted concentration of drug plus metabolites (level/dose ratio [LDR]) was defined as nonadherence. Nonadherence was also determined by clinician pill counts (CPC) of the proportion of prescribed pills that were unused and was defined as having greater than 30% of the prescribed pills remaining.

Results—LDR and CPC showed low concordance. LDR was unrelated to clinical response. CPC adherence was related to a higher response rate overall (adherent, 63.0% versus nonadherent, 47.2%, $p = .03$). Approximately half (50.8%) of the sample surveyed showed evidence of nonadherence by CPC. Neither measure of adherence was related to the occurrence of suicidal events or to the pace of decline in suicidal ideation.

Conclusions—Clinician pill counts may be a relevant measure of adherence that is related to outcome under formal clinical trial conditions in depressed adolescents. Nonadherence appears to be a common and significant source of treatment nonresponse.

Keywords

depression; medication adherence; antidepressants

The use of selective serotonin reuptake inhibitors (SSRIs) is recommended for the treatment of moderate-to-severe depression in youth.¹ Approximately 60% of depressed adolescents show a clinically significant response to an SSRI, and recent meta-analyses report a modest but increased risk for suicidal events compared with placebo.^{2,3}

Nonadherence to antidepressant treatment is a common occurrence in clinical samples of depressed patients and has been shown to be related to poor outcomes in depressed adults.^{4–6} Interventions to improve adherence to antidepressant medication have met with the greatest success in collaborative care models that target adherence and also promote optimal patient management.^{4,5,7–9} Only two studies, to our knowledge, have examined the relationship between adherence and clinical outcome in pediatric mood disorders.^{10,11} In a small, open trial of fluoxetine in depressed children and adolescents, there was a nonsignificant trend ($p < .08$) for an association between adherence and depressive symptom

reduction.¹⁰ Also, greater adherence was found to be associated with better outcomes in pediatric bipolar illness.¹¹ In the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study, we did find that lower plasma concentration was related to a decreased likelihood of response, at least in those participants treated with fluoxetine or citalopram, but did not examine the role of adherence in clinical outcomes.¹²

Nonadherence, besides leading to poor response, may also account for the increased risk for suicidal events found in adolescent patients, either by contributing to worsening depressive symptoms or because of the attendant withdrawal symptoms.^{3,13,14} Because adolescents metabolize some antidepressants faster than do adults, nonadherent adolescents could be particularly vulnerable to experiencing withdrawal effects, which, in turn could increase the risk for suicidal events.^{13,14}

One challenge to the study of adherence is its definition. Measures of adherence have relied on pill counts, patient self-report, medication diaries, electronic medical caps, and pharmacy refill records. At best, these measures show modest agreement.^{10,15–18} Adherence in both psychiatric and nonpsychiatric patients has also been determined through assessment of plasma levels of drug and metabolites, with nonadherence defined as either the absence of detectable drug, or having a high degree of variability of level to dose across assessments.^{6,19–21}

Given the paucity of information regarding adherence and outcome in pediatric mood disorders, we examined the relationship between adherence and clinical outcomes within the TORDIA sample, a randomized clinical trial to evaluate different treatment strategies for depressed adolescents who had not responded to an adequate trial with an SSRI. We used two different measures of adherence, namely clinician pill count (CPC) and variability in the ratio of plasma drug + metabolite concentration/ dose (level/dose ratio [LDR]). Based on the adolescent and adult literature, we hypothesized that: (1) poorer adherence would be associated with a lower rate of clinical response and less complete reduction in depressive symptoms; (2) in those treated with fluoxetine or citalopram, the relationship between adherence and outcome would be mediated by plasma drug concentration; and (3) poorer adherence would be associated with a higher rate of prospective suicidal events.

METHOD

The TORDIA trial was a randomized controlled trial with a clinical sample of 334 patients aged 12 through 18 years with a primary diagnosis of major depressive disorder (MDD), conducted at six US academic and community clinics from 2000 to 2006. Participants had a previous trial of at least 8 weeks with an SSRI and were still depressed. Entrants into the study were randomized to one of four treatments: switch to another SSRI, switch to venlafaxine XR (hereafter referred to as venlafaxine), switch to an SSRI plus cognitive behavior therapy (CBT), or switch to venlafaxine + CBT. We have previously reported that after 12 weeks of treatment, greater improvement was found in the combination of CBT plus medication switch, without differences among medication cells, and that no treatment differences were found with respect to suicidal events.^{22,23} Additional papers examined predictors and moderators of outcomes and longer-term course.^{24–26}

Of the 334 participants, 185 had blood levels of antidepressants obtained at 6 and at 12 weeks; an additional five individuals had only one blood level; because that level was zero, they were able to be classified as nonadherent and so were included. These 190 participants, compared with the remaining 144, were more likely to be responders at 12 weeks (105/190 [55.3%] versus 54/144 [37.5%], $\chi^2_1 = 10.36$, $p = .001$) and were less likely to have had a serious adverse event (9/190 [4.7%] versus 29/144 [19.4%], $\chi^2_1 = 17.99$, $p < .001$). They

were more likely to have completed treatment (181/190 [95.3%] versus 50/144 [34.7%], $\chi^2_1 = 140.77$, $p < .001$), and were more likely to attend the week 6 (185/190 [97.4%] versus 107/144 [74.3%]; $\chi^2_1 = 39.63$, $p < .001$) and week 12 clinical assessments (190/190 (100%) versus 97/144 [67.4%]; $\chi^2_1 = 72.17$, $p < .001$).

Inclusion and Exclusion Criteria

Participants had to have a DSM-IV²⁷ diagnosis of major depressive disorder with a Children's Depression Rating Scale—Revised (CDRS-R)²⁸ of ≥ 40 . Excluded were individuals with mania, psychosis, developmental disabilities, substance abuse or dependence, chronic disease, and those on a daily medication with psychotropic properties, except for participants who were on a stable dose of a stimulant for attention-deficit/hyperactivity disorder (ADHD). Also excluded were female participants who were either pregnant or lactating.

Assessment

The Child and Adolescent Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Versions (K-SADS-PL)²⁹ was used to ascertain DSM-IV diagnoses. Interview-rated depression was assessed using the CDRS-R. Self-reported depression, anxiety, hopelessness, suicidal ideation, drug and alcohol use, and family conflict were assessed via the Beck Depression Inventory³⁰ (BDI), Screen for Anxiety-Related Emotional Disorders (SCARED),³¹ Suicidal Ideation Questionnaire, Jr (SIQ-Jr),³² Beck Hopelessness Scale (BHS),³³ Drug Use Symptom Inventory (DUSI),³⁴ and Child Behavior Questionnaire, parent and child versions (CBQ-P and CBQ-A), respectively.³⁵ Two primary measures of response were used after 12 weeks of treatment: (1) at least a 50% reduction from baseline in the CDRS-R plus a Clinical Global Impressions Scale, Improvement subscale (CGI-I)³⁶ of ≥ 2 , corresponding to much or very much improved; and (2) slope of the CDRS-R over time, assessed at intake, 6 weeks, and 12 weeks. Suicidal adverse events were defined as new-onset or increase in suicidal ideation from baseline and/or an actual suicide attempt. A suicide attempt was defined as self-destructive behavior with at least implied intent to end one's life. Ratings for suicidal adverse events used the Brief Scale for Rating Severity of Suicidal Behavior (B-SSRS) with categories classified according to the Columbia Classification Algorithm for Suicide Assessment.³⁷ Interrater reliability was high for diagnoses (0.70) and for the CGI-I, CDRS-R, and the B-SSRS (ICCs > 0.90).

Treatment

Acute treatment consisted of 12 weeks of medication, monitored in nine pharmacotherapy sessions. Those randomized to CBT also received up to 12 weekly sessions. In the SSRI condition, participants were randomized to either fluoxetine or paroxetine for the first 181 participants, and after the Food and Drug Administration warning about paroxetine, citalopram was substituted for paroxetine for the remaining 153 participants. Those who received an SSRI were given 10 mg for the first week, 20 mg for the next 5 weeks, and at week 6, those who had not responded (CGI-I ≥ 4) were increased to 40 mg. Those who were treated with venlafaxine began with 37.5 mg for 1 week, and their dose was increased by 37.5 mg each week for the next 3 weeks, until a target dose of 150 mg was reached. Participants who did not show a response were increased to 225 mg at 6 weeks. By the end of 12 weeks, the mean doses were 33.8 mg (95% CI: 32.0 to 35.6) for SSRI and 205.4 mg (95% CI: 199.0 to 211.7) for venlafaxine.

Adherence Definitions

Adherence was evaluated by examining variation, between 6 and 12 weeks, in the ratio of the plasma concentration of drug + metabolite divided by dose (level-dose ratio [LDR]).

Nonadherence was defined as either having at least one plasma drug concentration of zero, or a twofold or greater variation in the LDR between the two assessment points, consistent with the variation in levels found in nonadherent participants in other studies, which we refer to as the LDR index (LDRI).^{19,21} Because of an oversight, time of last dosage was not routinely recorded. There was no evidence of order effects within the LDRI; that is, the response rate was not different in those with LDRI of 0.5 (16/24 [66.7%]) versus LDRI 2.0 (11/21 [52.4%], $\chi^2_1 = 0.95$, $p = .33$), nor were there statistically significant differences within each medication or medication class ($p > .25$). Therefore, the data for those with 0.5 and 2.0 LDRI's were combined and compared with those with intermediate LDRI's ($0.5 < \text{LDRI} < 2.0$). The data were reanalyzed with an LDRI of 1.5-, three-, and fourfold variation, with no substantial changes in the results, although the small number of those with threefold ($n = 41$) and fourfold variation ($n = 32$) precluded some analyses. Adherence was also determined by clinician count of pills (CPC) that remained in the participants' medication containers at each pharmacotherapy session. The ratio of the total number prescribed minus the number remaining/total prescribed was used to estimate adherence. We defined adherence as use of at least 70% of prescribed medication as has been done in some other studies.³⁸ The CPC was assessed at each pharmacotherapy visit, which took place weekly for the first 6 weeks, and then bi-weekly for the next 6 weeks. A high proportion of participants brought pills in for the CPC across sessions (91.8%).

Plasma Level Determination

In the TORDIA trial, metabolites as well as levels of the parent compound were measured, namely Odesmethylvenlafaxine (ODV) and norfluoxetine (NF) for venlafaxine and fluoxetine, respectively. Neither paroxetine nor citalopram had any active metabolites, and consequently levels of only the parent compound were measured.

Plasma concentrations of the medications and their metabolites were determined through venous blood samples collected at week 6 and week 12, at least 2 weeks after medication dose adjustment. The samples were centrifuged immediately after collection, packed with dry ice, and sent to the Geriatric Psychopharmacology Laboratory at the University of Pittsburgh directed by Bruce G. Pollock, M.D., Ph.D.

Paroxetine and citalopram were measured by reverse-phase high-performance liquid chromatography (HPLC) using previously developed methods.^{39,40} The assay for paroxetine is linear in the range of 5 to 200 ng/mL with interassay variability of 3.4% to 5.4%. The assay for citalopram is linear in the range of 2.5 to 500 ng/mL with interassay variability of 2.9% to 3.93%. Methods to measure fluoxetine, norfluoxetine (NF), venlafaxine, and O-desmethylvenlafaxine (ODV) concentrations were developed by the laboratory of Dr. Pollock. Plasma was alkalized using carbonate buffer (pH 10.7), extracted using ethyl acetate in heptane (2:8), and back-extracted into 0.025 mol/L potassium phosphate (pH 2.4). Fluoxetine and active metabolite, NF, were measured using reverse-phase HPLC using ultraviolet detection at 205 nm. Samples were evaporated and reconstituted in 0.125 mL potassium phosphate (pH 2.4). Separation was completed on an Ultrasphere C18 (Beckman Coulter, Brea, CA), 5- μ m HPLC column, 150 $\times$ 2 mm with a flow rate of 0.35 mL/min at room temperature. The assay is linear in the range from 3 to 500 ng/mL with interassay variability of 6.0% to 7.0% for fluoxetine and 5.0% to 7.0% for NF. Venlafaxine and active metabolite, ODV, were measured using reverse-phase HPLC with ultraviolet detection at 225 nm. Samples were evaporated and reconstituted in 0.025 mol/L potassium phosphate (pH 2.4). Separation was completed on a Nucleosil-100 C18 (Machery Nagel, Bethlehem, PA), 5- μ m HPLC column, 120 mm $\times$ 4.6 mm with a flow rate of 1.0 mL/min. The assay is linear, from 5 to 1,000 ng/mL for venlafaxine and ODV, with an interassay variability of 2.5% to 6.8%. Clomipramine was used as the internal standard for

paroxetine, fluoxetine, and NF. Paroxetine was used as the internal standard for citalopram, and 9-OH risperidone was used for venlafaxine and ODV.

Statistical Analysis

Agreement between the two measures of adherence was assessed using the kappa statistic, which takes into account agreement that occurs beyond chance.⁴¹ Demographic and clinical correlates of each of these measures of adherence were assessed using standard univariate statistics, as were the relationship between each of these measures of adherence and outcome. In addition, the CPC measure was grouped into quartiles, and the relationship between adherence and outcome was examined using a Chi-square test of trend overall, and then under conditions of low and high LDR.

Mixed regression models were conducted to examine whether either LDR or CPC measures of adherence were significantly associated with change in the slope of the CDRS-R or the SIQ-Jr. The model included a fixed effect for adherence (which estimates the average intercept for the adherent and nonadherent groups), a random effect for time (which estimates the rate of change in the CDRS-R or SIQ-Jr over time), and an interaction term (which estimates the specific rate of change for each group over time). Time was defined as natural log of weeks since baseline + 1. The data analysis was done using PASW Statistics 18.0.2 (SPSS Inc., Chicago, IL) and STATA 9.2 (Stata Corp., College Station, TX) statistical software. Because of the exploratory nature of these analyses, the alpha value was set at 0.05 without correction for multiple comparisons.

RESULTS

Frequency of Nonadherence: Concordance Between Measures

Of the 190 participants, 181 had CPCs, of whom 92 of 181 (50.8%) were rated as adherent (pills ratio = 70%). Nearly 64% (121/190) were rated as adherent by the LDR measure. After correcting for chance agreement, the concordance between these two measures was very low (percent agreement, 48.6%, $\kappa = 0.03$, 95% CI: -0.17 to 0.11, $p = .65$) (Table 1).

Relationship between Adherence and Drug Concentration Levels

Participants who were adherent by LDRI had a higher drug + metabolite concentration level at both weeks 6 (standardized score, 0.24 [SD = 0.89] versus -0.47 [SD = 1.07], Mann-Whitney U = 2216.50, $p < .001$), and 12 (0.31 [0.91] versus -0.54 [0.98], U = 1908.5, $p < .001$). However, consistent with the definition, a higher LDRI was associated with a higher plasma drug concentration at time 12 (standardized concentration, LDRI = 2.0, [0.5 {1.0}] versus LDRI = 0.5 [-0.82 {0.5}]), Mann-Whitney U = 74.0, $p < .001$). There was no association between the CPC measure and plasma concentration (standardized score -0.0004 [SD = 1.05] versus -0.02 [SD = 0.98], Mann-Whitney U = 3920.00, $p = .91$). Also, there was no relationship between CPC adherence quartile and plasma level overall, or for any medication class (Spearman's rho: -0.14 to 0.09, $p > .44$).

Relationship of Demographic and Clinical Variables at Intake to Adherence

As determined by the LDRI, adherent patients were slightly older (16.0 [SD=1.6] years versus 15.4 [SD= 1.4] years; $t = -2.29$, $df=188$, $p=.02$) and had lower rates of ADHD (7.5% versus 17.4%, $\chi^2_1 = 4.34$, $p = .04$). No demographic or clinical variables were observed to be related to the CPC.

Relationship Between Adherence and Outcomes

Clinical Response—There was no relationship observed between response and LDRI overall (adherent 67/121 (55.4%) versus nonadherent, 27/45 (60.0%), $\chi^2_1 = 0.29$, $p = .59$), or within each medication class and individual medication ($p > .07$) (Table 2).

There was a higher rate of response among those who were rated adherent based on the CPC (58/92 [63.0%] versus 42/89 [47.2%], $\chi^2_1 = 0.60$, $p = .03$; χ^2_1 test for trend = 3.72, $p = .054$). This association was significant among those treated with SSRIs (31/49 [63.3%] versus 18/42 [42.9%], $\chi^2_1 = 3.79$, $p = .05$; test for trend, $\chi^2_1 = 4.19$, $p = .04$), with similar, but nonsignificant relationships for each of the three SSRIs ($p > .07$; Figure 1). There was no association between CPC adherence and response for venlafaxine (27/43 [62.8%] versus 24/47 [62.8%], $\chi^2_1 = 1.26$, $p = .26$; test for trend, $\chi^2_1 = 0.34$, $p = .56$).

There was no relationship between LDR-defined adherence and continuous outcome on the CDRS-R (adherence by log-time, $p > .82$). However, there was a marginally significant relationship between CPC and change on the CDRS-R (log-time by adherence interaction ($\beta = -1.38$, $z = -1.94$, $p = .052$), meaning that greater adherence was associated with a more rapid improvement in symptoms. The relationship was significant for venlafaxine ($\beta = -1.91$, $z = -2.03$, $p = .04$); similar, but nonsignificant trends were found for analyses by individual SSRIs ($p > .06$).

Mediation of Adherence Findings by Drug Concentration—Although CPC-defined adherence was related to outcome in those treated with citalopram or fluoxetine, it was not related to citalopram or fluoxetine exposure, so mediation of the effects of adherence on plasma antidepressant + metabolite level could not be tested.⁴²

Suicidal Adverse Events—There was no relationship between LDR measures of adherence and suicidal adverse events (adherent, 4/69 [12.4%] versus nonadherent, 15/121 [5.8%], $\chi^2_1 = 2.13$, $p = .15$). This was true both for SSRIs (6/69 [8.7%] versus 2/28 [7.1%], FET $p > .99$) and for venlafaxine (9/52 [17.3%] versus 2/41 [4.9%]; Fisher's exact test, $p = .10$). There was also no relationship between CPC-defined adherence and suicidal events overall (10/92 [10.9%] versus 9/89 [10.1%], $\chi^2_1 = 0.03$, $p = .87$), or by medication type (SSRI: 4/49 [8.2%] versus 4/42 [9.5%], FET $p > .99$; venlafaxine, 6/43 [14.0%] versus 5/47 [10.6%], $\chi^2_1 = 0.23$, $p = .63$). There was also no association between either measure of adherence and change in suicidal ideation over time (adherence by log-time, $p = .31$ and $p = .16$ respectively).

Relation of Adherence to Assigned Treatment—LDR-determined adherence was higher in those assigned to SSRIs than those assigned to venlafaxine (71.1% versus 55.9%, $\chi^2_1 = 4.76$, $p = .03$). The LDRI adherence rates showed a nonsignificant trend towards being lower in those also treated with CBT in combination with medication (57.3% versus 69.3%, $\chi^2_1 = 2.95$, $p = .09$). By CPC, there were no statistically significant differences in the rates of adherence between SSRI and venlafaxine (53.8% versus 47.8%, $\chi^2_1 = 0.67$, $p = .41$) or between those treated with CBT and those in the medication-only group (52.4% versus 49.5%, $\chi^2_1 = 0.15$, $p = .70$). There was no difference either in the LDR adherence rates between those receiving a stimulant versus not (52.4% versus 65.1%, $\chi^2_1 = 1.30$, $p = .25$) or in the LDRI (1.01 [0.63] versus 1.28 [SD = 1.30], $U = 1,104.00$, $p = .24$). The rate of CPC-rated adherence was higher in those also receiving a stimulant (15/21 [71.4%] versus 77/160 [48.1%], $\chi^2_1 = 4.03$, $p = .045$).

DISCUSSION

We found that the two measures of adherence used in this study, LDR and CPC, showed no more than chance agreement. Higher LDR-rated adherence was related to higher plasma levels of drug + metabolite but was unrelated to response. A CPC ratio of at least 70% was associated with clinical response. Also, response was related to CPC-defined adherence in a dose-response fashion. Approximately half of the sample (50.8%) showed adequate adherence according to the CPC definition. Nonadherence, defined either by LDR or CPC, was unrelated to the occurrence of suicidal adverse events. We discuss these findings in the context of the extant literature after first reviewing the limitations of this study.

This study has several limitations. Plasma levels of adherence were not obtained on all participants, and the subgroup that did provide such levels had higher rates of response and of study completion, and lower rates of adverse events, restricting the range of participant variability on these outcomes. Similarly, the subgroup that provided plasma levels also was much more consistent in providing CPC data. Furthermore, we obtained only two plasma levels over the course of the study. Plasma levels were not necessarily trough levels, and the time when they were drawn was not systematically assessed, although the literature emphasizes that estimates of dose times by participants are often inaccurate.^{43,44} Therefore, some of the variability in plasma concentration could be due to timing of the blood draw relative to the last dose, or to differences in rate of drug metabolism, rather than adherence per se. For this reason, we conducted sensitivity analyses that showed similar results across a wide range of LDR variability. Paroxetine shows nonlinear pharmacokinetics, meaning that a given dose increase could result in an increase in drug concentration more so in this drug than in the other study medications.¹⁴ However, the dosage range for those treated with paroxetine was very narrow (mean 34.3 mg, 95% CI: 31.1 to 37.4, range 20 to 40), somewhat mitigating this effect. Clinician-rated measures are dependent upon the participants actually bringing all prescribed medication in with them to their pharmacotherapy sessions. Validation of adherence using electronic medication caps or pharmacy records could have enhanced the reliability and the generalizability of these findings, as comparative studies show that clinician-based ratings of adherence overestimate adherence relative to electronic medication caps.^{10,18,20,38,43} Finally, because of the exploratory nature of these analyses, the alpha value was set at 0.05, without correction for multiple contrasts.

We found low agreement between the two measures, perhaps in part because of the above-noted limitations. Also, the CPC was based on up to nine clinician ratings over 12 weeks, whereas the LDR was based on just two points in time. Low agreement between patient-reported adherence and direct measurement of drug concentration or variability have previously been reported.^{21,45} Pill counts correlate well with prescription claims data, but are less accurate than electronic medication-event monitoring, and have been shown to have a wide range of correlations with pharmacokinetic measures of adherence from negligible to high.^{15,18,21,46–49}

Consistent with other studies, we found that clinician pill counts showed a modest dose–response relationship to outcome, with a higher rate of response in those participants who had 30% or less of their medication remaining.⁴ LDR may not have been related to outcome both because we did not have data on time since last dose and because the absolute concentration, at least for citalopram and fluoxetine, may be more relevant to clinical response than the variability between concentrations.¹² In particular, we previously found that when the exposure was low at 6 weeks and the dose was increased, if the level was increased at 12 weeks, there was a higher probability of response than in individuals whose levels did not change. Thus, for a subgroup of participants, reaching a certain level of

exposure was more important for achieving response than maintaining a consistent but low level of drug concentration. The relationship between CPC and outcome was not affected by the half-life of antidepressant medication, as we had very similar findings for those treated with a drug with a long half-life (fluoxetine) and for participants treated with a drug with a much shorter half-life (citalopram).¹⁴ However, in this study, we were not able to show a clear relationship between CPC and citalopram or fluoxetine plasma levels. Greater variability in drug concentration (e.g., higher LDR variation) was found in younger participants and those with ADHD. It is possible that both of these characteristics contributed to youth being more erratic in taking their medication, or that these factors are proxies for variation in drug metabolism. Conversely, CPC-rated adherence was greater in youth who were taking stimulants, perhaps because stimulants helped to mitigate against forgetfulness in taking medication. Also, parents and youth were already being attentive to taking one class of medication, possibly making adherence for a second medication more likely. This suggests that parents should monitor adherence to antidepressant medication in depressed youth, particularly closely in younger adolescents, and in those who are distractible and forgetful.

Neither measure of adherence was related to the incidence of suicidal events, thus failing to support the view that suicidal events in depressed adolescents occur due to nonadherence. Because one hypothesis advanced is that nonadherence would be particularly deleterious in those participants treated with drugs with a shorter half-life, we examined these findings by medication, and still did not find an association between nonadherence and suicidal outcomes.¹³

In summary, we found a modest relationship between the degree of CPC ratings of adherence, and clinical outcome on both dichotomous and continuous measures of depression. Pill counts may have some utility in monitoring adherence and improving outcome, but future studies of adherence should also use other methods, such as electronic medication caps or pharmacy records. Although LDRI per se was unrelated to outcome, we have previously shown that the absolute level of drug + metabolite predicts treatment response in treatment resistant youth, particularly those treated with citalopram or fluoxetine.¹² These results support further investigation of the relationship between adherence to antidepressant medication and response in depressed adolescents. Because nonadherence appears to be very common and may be an important contributor to nonresponse in adolescent depression, interventions designed to improve adherence may improve clinical outcomes in depressed adolescents.

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FIGURE 1.

Dose-response between clinician-rated adherence and clinical response.

Note: χ^2 tests for trend:

All: $\chi^2_1 = 3.72$, $p = .05$; venlafaxine (VLX): $\chi^2_1 = 0.34$, $p = .56$; selective serotonin reuptake inhibitor (SSRI): $\chi^2_1 = 4.19$, $p = .04$; paroxetine (PAR): $\chi^2_1 = 0.00$, $p > .99$; citalopram (CIT): $\chi^2_1 = 6.00$, $p = .01$; fluoxetine (FLX): $\chi^2_1 = 2.06$, $p = .15$.

LDR = level/dose ratio (ratio of drug + metabolites/dose between two levels).

TABLE 1

Adherence by Clinician Pill Count (CPC) and Level/Dose Ratio Index (LDRI) (N = 181)

		LDRI	
		-	+
CPC	-	31	58
	+	35	57

Note: LDRI indicates ratio of drug + metabolites/dose between two levels. + = adherent; - = non-adherent.

TABLE 2

Level-Dose Ratio Index (LDRI) and Clinical Response (%) Overall and by Individual Medication

LDRI	0.5 OR	2.0	< 0.5 AND > 2.0	Test	df	p
Overall	60.0		55.4	$\chi^2 = 0.29$	1	.59
Paroxetine	57.1		41.7	FET	-	.65
Citalopram	75.0		60.0	FET	-	>.99
Fluoxetine	22.2		59.5	FET	-	.07
Venlafaxine	72.0		53.9	$\chi^2 = 2.31$	1	.13

Note: LDRI indicates ratio of drug + metabolites/dose between two levels. FET = Fisher's exact test.