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Antidepressant Exposure as a Predictor of Clinical Outcomes in the Treatment of Resistant Depression in Adolescents (TORDIA) Study

Dara J. Sakolsky, MD, PhD[*], **James M. Perel, PhD**[*], **Graham J. Emslie, MD**[†], **Gregory N. Clarke, PhD**[‡], **Karen Dineen Wagner, MD, PhD**[§], **Benedetto Vitiello, MD**[||], **Martin B. Keller, MD**[¶], **Boris Birmaher, MD**[*], **Joan Rosenbaum Asarnow, PhD**[L], **Neal D. Ryan, MD**[*], **James T. McCracken, MD**[L], **Michael J. Strober, PhD**[L], **Satish Iyengar, PhD**[**], **Giovanna Porta, MS**[*], and **David A. Brent, MD**[*]

[*]Western Psychiatric Institute and Clinic, Pittsburgh, PA

[†]Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas, TX

[‡]Kaiser Permanente Center for Health Research, Portland, OR

[§]Department of Psychiatry & Behavioral Health Sciences, The University of Texas Medical Branch, Galveston, TX

[||]National Institute of Mental Health, Bethesda, MD

[¶]Department of Psychiatry & Human Behavior, Brown University-Butler Hospital, Providence, RI

[L]Department of Psychiatry, University of California, Los Angeles, CA

[**]Departments of Statistics and Psychiatry, University of Pittsburgh, Pittsburgh, PA

Abstract

This paper examines the relationship between plasma concentration of antidepressant and both clinical response and adverse effects in treatment-resistant depressed adolescents. Adolescents (n = 334) with major depression who had not responded to a selective serotonin reuptake inhibitor (SSRI) were randomized to 1 of 4 treatments: switch to another SSRI (fluoxetine, citalopram, or paroxetine), switch to venlafaxine, switch to SSRI plus cognitive behavior therapy, or switch to

Corresponding Author: David A. Brent, MD, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Room 315, Bellefield Towers, 3811 O'Hara St, Pittsburgh, PA 15213, brentda@upmc.edu.

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AUTHOR DISCLOSURE INFORMATION

Dr Birmaher has participated in forums sponsored by Solvay Pharmaceuticals, Inc and Abcomm, Inc. He gave a presentation on bipolar disorders in children at a meeting sponsored by Solvay. Dr Birmaher also received royalties from Random House, Inc. Dr Emslie receives research support from Biobehavioral Diagnostics Inc, Forest Laboratories, Shire and Somerset, and is a consultant for Biobehavioral Diagnostics, Inc, Eli Lilly, Forest Laboratories, Inc, Pfizer, Inc, Shire, Validus Pharmaceuticals, and Wyeth Pharmaceuticals. Dr Keller has served on advisory boards for Abbott Laboratories, Bristol-Myers Squibb, CENEREX, Cyberonics, Cypress Bioscience, Forest Laboratories, Janssen, Novartis, Organon, and Pfizer. Dr Perel is a consultant and expert witness for a consortium of 10 pharmaceutical companies. No other financial disclosures were reported. Dr Asarnow has consulted on cognitive-behavior therapy and quality improvement for depression and received unrestricted research funding from Philip Morris USA. Dr Wagner reported (July 2005 to July 2010) that she has received research support from AstraZeneca, Eli Lilly, Johnson & Johnson, National Institute of Mental Health, and Organon, and was a consultant/advisory board member for Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen, Jazz Pharmaceuticals, Novartis, Ortho-McNeil, Pfizer, Organon, Otsuka, Solvay, and Wyeth Ayerst.

venlafaxine plus cognitive behavior therapy. Adolescents who did not improve by 6 weeks had their dose increased. Plasma concentrations of medication and metabolites were measured at 6 weeks in 244 participants and at 12 weeks in 204 participants. Adolescents treated with citalopram whose plasma concentration was equal to or greater than the geometric mean (GM) showed a higher response rate compared to those with less than the GM, with parallel but nonsignificant findings for fluoxetine. A dose increase of citalopram or fluoxetine at week 6 was most likely to result in response when it led to a change in concentration from less than the GM at 6 weeks to the GM or greater at week 12. Plasma levels of paroxetine, venlafaxine, or O-desmethylvenlafaxine were not related to clinical response. Exposure was associated with more cardiovascular and dermatologic side effects in those receiving venlafaxine. Antidepressant concentration may be useful in optimizing treatment for depressed adolescents receiving fluoxetine or citalopram.

Keywords

major depressive disorder; adolescents; plasma concentration; drug exposure; optimization

Clinical guidelines recommend the use of antidepressants for adolescents with moderate to severe depression.[1] Nevertheless, only approximately 60% of depressed adolescents respond to an initial trial with a selective serotonin reuptake inhibitor (SSRI), and only half of those who do not respond to an initial SSRI trial will respond to a second antidepressant trial.[2,3] Therapeutic drug monitoring has been advocated as one means of improving clinical outcome in patients treated with antidepressants, as individual differences in pharmacokinetics may contribute substantially to variability in clinical response.[4]

The relationship between SSRI or serotonin-norepinephrine reuptake inhibitors (SNRI) exposure and clinical response has not been carefully studied in adolescents, despite their widespread use. Although many studies in depressed adults find no relationship between drug concentration and response to SSRIs or SNRIs,[5,6] several reports have found a positive association between greater antidepressant concentration and the likelihood of response.[7–10] A relationship between drug concentration and antidepressant response has been reported in depressed youth treated with other classes of antidepressants (eg, tricyclic antidepressants and bupropion).[11,12]

Despite mixed findings in adult studies, the study of the relationship between drug concentration and outcome in adolescent samples has also been advocated by some experts because of developmental differences between adults and adolescents in drug metabolism and drug response.[13,14] Specifically, adolescents metabolize several commonly used antidepressant agents, such as citalopram, sertraline, and venlafaxine, more rapidly than adults.[13,15] Furthermore, a study that measured antidepressant drug concentration simultaneously with serotonin transporter binding in vivo suggests that drug concentrations are important given that, within a certain range, increasing plasma concentration of an SSRI or SNRI will increase serotonin transporter occupancy, which in turn increases the likelihood of response.[16]

Consequently, we examined the relationship between plasma antidepressant concentration and clinical response in the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) clinical trial. In this study, 334 depressed adolescents who had not responded to a treatment with an SSRI of at least 8 weeks' duration were randomized to 1 of 4 groups: switch to another SSRI (either fluoxetine, paroxetine, or citalopram), switch to venlafaxine, switch to another SSRI plus cognitive behavior therapy (CBT), or switch to venlafaxine and CBT. After 12 weeks of treatment, those who received CBT and either of the 2 medication switch strategies showed modestly better clinical response rate than those who received

medication alone, with no difference between SSRI or venlafaxine.[3] Plasma concentrations of drug and active metabolites were obtained at 6 and 12 weeks. We hypothesized that: (1) higher drug plus active metabolite concentrations at 6 weeks would be associated with higher rates of treatment response at 12 weeks; (2) a dose increase at 6 weeks would be more likely to result in response if exposure was increased by 12 weeks; and (3) higher drug levels would be associated with greater rates of adverse effects and adverse events.

METHODS

Participants

As described previously, study participants were 334 adolescents aged 12 to 18 years with moderately severe (Clinical Global Impression V Severity [CGI-S] subscale ≥4 and a Children's Depression Rating Scale Revised [CDRS-R] ≥40)[17,18] major depressive disorder that did not respond to treatment with an SSRI of at least 8 weeks, with the last 4 weeks at a dose of at least 40 mg of fluoxetine or its equivalent (eg, 40 mg of paroxetine, 40 mg of citalopram, 20 mg of s-citalopram, or 150 mg of sertraline).[3] Excluded were participants with the diagnoses of bipolar spectrum disorder, psychosis, pervasive developmental disorder or autism, substance abuse or dependence, eating disorders, or hypertension (diastolic blood pressure ≥90 mm Hg). Other exclusionary criteria include history of nonresponse to CBT (≥7 sessions) or venlafaxine (at least 4 weeks at ≥150 mg/d); 2 or more adequate trials of an SSRI, or use of antipsychotics, mood stabilizers, or other classes of antidepressants. Females who were pregnant, breastfeeding, or were sexually active and not using contraception were also excluded. Informed assent/consent was obtained from participants and families. This study was approved by the institutional review boards of all 6 sites.

Interventions

Participants were randomly assigned to 12 weeks of treatment, which included either switch to a different SSRI, switch to different SSRI plus CBT, venlafaxine, or venlafaxine plus CBT. All participants received family psychoeducation and supportive management. Those assigned to CBT received on average 8.3 sessions (SD = 3.6). Participants previously treated with fluoxetine and randomized to an SSRI switch received paroxetine and vice versa. Participants previously treated with other SSRIs (eg, sertraline) and randomized to an SSRI switch were assigned to either fluoxetine or paroxetine. Owing to international concerns about the safety and efficacy of paroxetine that emerged midway through the study, after 181 participants had been enrolled, citalopram was substituted for paroxetine in the protocol. The dosage schedule for all of the SSRIs began with 10 mg per day for the first week, 20 mg for weeks 2 to 6, with an optional increase to 40 mg at week 6 if there was inadequate clinical improvement (CGI Improvement subscale [CGI-I] ≥4).[17] Those assigned to venlafaxine received 37.5 mg for week 1, and for weeks 2 to 4, they received 75 mg, 112.5 mg, and 150 mg, respectively, with an optional increase from 150 to 225 mg at week 6. From 6 week through week 12, the average daily doses of study medications were as follows: paroxetine, 35.2 mg (SD = 8.7); citalopram, 31.2 mg (SD = 10.1); fluoxetine, 33.8 mg (SD = 9.3); and venlafaxine, 200.9 mg (SD = 35.2).

Assessments

The TORDIA had one primary continuous measure, change on the CDRS-R, and one primary dichotomous outcome, "adequate clinical response," defined as a CGI-I score of 2 or less (improved or very much improved), a decrease in the CDRS-R score by at least 50%, and a 12-week CDRS-R of less than 40. Clinical response is the outcome used in this paper, as it was with this measure that treatment effects were detected.[3] Adverse effects were defined as any complaint reported to the pharmacotherapist and were systematically

monitored with the Side Effects Form for Children and Adolescents (SEFCA).[19] Suicidal events were monitored by a spontaneous report for the first 181 participants and, subsequently, were rated weekly using the Brief Suicide Severity Rating Scale.[20]

Adverse events were defined as new onset or worsening of symptoms and were elicited by clinical interview. Serious adverse events were those that led to significant disability, were life-threatening, or resulted in hospital care.

Plasma Concentrations

Venous blood samples were obtained to determine plasma concentrations of the medications and their metabolites at 6 (ie, before the optional increase in dose) and 12 weeks. Plasma concentrations were obtained in 244 (73%) of TORDIA participants at week 6 and 204 (59.9%) at week 12; 185 participants provided samples at both time points. Week 6 drug concentrations were used as an estimate of overall exposure and were strongly correlated with week 12 levels (rs = 0.48–0.83, all Ps < 0.005). Participants from whom plasma concentrations were not obtained were less likely to respond to treatment (36.7% vs 51.6%; $\chi^2_1 = 5.91$, P = 0.02), more likely both to have had a serious adverse event (20.0% vs 7.8%; $\chi^2_1 = 9.96$, P = 0.002), and to have left the study before week 6 (73.9% vs. 1.3%; Fisher exact test, P < 0.001).

Participants were instructed to hold the morning dose of medication on the day of blood draw to obtain trough levels. Once collected, samples were centrifuged immediately, packed with dry ice, and sent to the Geriatric Psychopharmacology Laboratory at the University of Pittsburgh directed by Bruce G. Pollock, MD, PhD.

Paroxetine and citalopram were measured by reversed-phase high-performance liquid chromatography (HPLC) using previously developed methods.[21,22] The assay for paroxetine is linear in the range of 5 to 200 ng/mL, with an 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 of potassium phosphate, pH 2.4. Separation was completed on an Ultrasphere C18 (Beckman Coulter, Brea, Calif), 5-Km HPLC column, 150 × 2 mm with a flow rate of 0.35 mL/min at room temperature. The assay is linear in the range of 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 reversephase 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 (Macherey Nagel, Bethlehem, Pa), 5-Km HPLC column, 120 × 4.6 mm, with a flow rate of 1.0 mL/min. The assay is linear from 5 to 1000 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

For medications with active metabolites, drug exposure was examined for drug, active metabolite, and the sum of drug and active metabolite level (ie, fluoxetine + N For venlafaxine +ODV). The geometric mean (GM), rather than the arithmetic mean, was used

to evaluate the relationship between drug concentration and response because this relationship is usually characterized by a log-normal distribution. To calculate the geometric mean, zero levels were replaced with n j 1 where n equals the lower linear limit for the given assay. The relationship between drug concentration and response was assessed by comparing the log of the GMs of the responders and the nonresponders using the Mann-Whitney U test. The relationship between exposure and response, adverse effects, and adverse events were also assessed by comparing the rates of clinical outcomes in those greater than and less than the GM for paroxetine, citalopram, fluoxetine plus NF, and venlafaxine plus ODV using the χ^2 test or the Fisher exact test. Logistic regression was used to assess the relationship of drug exposure (converted to standardized units of the log of the GM) and response, after controlling for CBT treatment and dose increase at 6 weeks. The relationship between response and change in the exposure between 6 and 12 weeks was assessed using the Fisher exact test among nonresponders at 6 weeks whose dose was increased. Analyses were conducted using PASW Statistics 18.0 (SPSS Inc, Chicago, Ill) and Stata Statistical Software 9.2 (StataCorp LP, College Station, Tex).

RESULTS

Clinical Response and Exposure at Week 6

The arithmetic mean and standard deviation (SD) as well as the GM and 90% confidence interval (CI) for each drug, active metabolite, and their sum are presented for all subjects, responders, and nonresponders in Table 1. There were no differences between the GMs of responders and nonresponders for any drug (paroxetine, P = 0.33; citalopram, P = 0.15; fluoxetine, P = 0.22; venlafaxine, P = 0.60), active metabolite (norfluoxetine, P = 0.20; ODV, P = 0.15) or sum (fluoxetine + norfluoxetine, P = 0.16; venlafaxine + ODV, P = 0.12). Participants treated with citalopram whose 6-week drug concentration was equal to or greater than the GM showed a higher rate of response (13/17 [76.5%]) compared with the patients with a drug concentration less than the GM (3/10 [30.0%]; Fisher exact test, P = 0.04). A similar but nonsignificant trend was found in youth treated with fluoxetine (fluoxetine, 25/43 [58.1%] vs 7/21 [33.3%], $\chi^2_1 = 3.47$, P = 0.06; fluoxetine + norfluoxetine 23/39 [59.0%] vs 9/25 [36.0%], $\chi^2_1 = 3.22$, P = 0.07). Response rates were not significantly different for participants treated with paroxetine or velafaxine whose week 6 levels were equal to or greater than the GM versus less than the GM (paroxetine, 7/20 [35.0%] vs 6/14 [42.9%]; $\chi^2_1 = 0.22$, P = 0.64; venlafaxine, 38/69 [55.1%] vs 27/50 [42.9%]; $\chi^2_1 = 0.01$, P = 0.91; ODV, 40/80 [50.0%] vs 25/39 [64.1%]; $\chi^2_1 = 2.10$, P = 0.15; venlafaxine + ODV, 38/75 [50.75%] vs 27/44 [61.4%]; $\chi^2_1 = 1.28$, P = 0.26).

Using logistic regression to control for the effects of CBT and of a dose increase, there was a significant relationship between exposure at week 6 and the outcome at week 12 for the fluoxetine/citalopram group (OR = 2.12; 90% CI, 1.26–3.57) but not for the paroxetine (OR = 0.65, 90% CI, 0.32–1.34) or the venlafaxine group (OR = 0.76; 90% CI, 0.54–1.05).

Impact of Dose Increase on Exposure at Week 12 and Response

Approximately two thirds (68.4%) of the participants from whom week 6 plasma concentrations were obtained had a dose increase at 6 weeks. There was a relationship between the dose (mg/kg) at 12 weeks and drug concentration for both those treated with SSRIs (r = 0.51, df = 91, P < 0.001) and with venlafaxine (r = 0.46, df = 88, P < 0.001). The participants treated with citalopram or fluoxetine who received a dose increase and whose drug exposure changed from less than the GM at 6 weeks to equal to or greater than the GM at 12 weeks were much more likely to respond than were the participants whose exposure at 12 weeks continued to be less than the GM (6/12 [50.0%] vs 0/10 [0.0%]; Fisher exact test, P = 0.02). In contrast, those treated with citalopram or fluoxetine whose 6-week level was

equal to or greater than the GM showed no difference in response rates to a dose increase whether their 12-week exposure was greater than or less than the GM (17/26 [65.4%] vs 1/1 [100.0%]; Fisher exact test, P > 0.99). Those treated with venlafaxine whose week 6 exposure level was less than the GM showed no difference in response rates to a dose increase whether their 12-week exposure was greater or less than the GM (8/14 [57.1%] vs 5/10 [50.0%]; Fisher exact test, P > 0.99). Likewise, those participants treated with venlafaxine who received a dose increase but whose week 6 levels were equal to or greater than the GM showed no difference in response rates to a dose increase whether their 12-week exposure was greater or less than the GM (20/37 [54.1%] vs 2/6 [33.3%]; Fisher exact test, P = 0.41).

Adverse Effects, Adverse Events, and 6-Week Exposure

The relationship between adverse effects, adverse events, and exposure was examined in each SSRI individually. Because the relationships were similar across individual drugs, the results for the 3 SSRIs were combined. Adverse effects were reported equally among those with SSRI exposure equal to or greater than the GM and those with SSRI exposure less than the GM (Table 2). Among those treated with venlafaxine, higher exposure was associated with dizziness when standing up (54.7% vs 27.3%; $\chi^2_1 = 8.43$, P = 0.004), cardiovascular (61.3% vs. 31.8%; $\chi^2_1 = 9.66$, P = 0.002), and dermatologic adverse effects (41.3% vs 20.5%; $\chi^2_1 = 5.42$, P = 0.02) Among the participants who received either SSRIs or venlafaxine, the high and low exposure groups were not different with respect to rates of adverse events, serious adverse events, or self-harm events.

DISCUSSION

In this study of adolescents with treatment-resistant depression, no association was found between mean plasma concentration at 6 weeks and response rates at 12 weeks. However, adolescents treated with citalopram whose plasma concentration was equal to or greater than the GM showed a higher response rate compared to those treated with citalopram whose plasma concentration was less than the GM. A similar but nonsignificant trend was found in youth treated with fluoxetine. In addition, a dose increase that resulted in an increase in exposure from less than the GM at 6 weeks to exposure equal to or greater than the GM at 12 weeks was also associated with a greater likelihood of response in those treated with either citalopram or fluoxetine. Taken together, these observations suggest the possibility of a threshold for optimal clinical benefit in some adolescents treated with either citalopram or fluoxetine. Drug concentration was not a strong determinant of adverse events, although higher venlafaxine plus ODV levels were associated with cardiovascular and other adverse effects. We first review the limitations and strengths of this study, place the findings placed in the context of the extant literature, and discuss clinical and research implications.

The major limitation of this study is that the measurement of drug exposure was added onto this clinical trial, which was not itself designed to assess the relationship between drug exposure and outcome. The ideal study examining the relationship between drug exposure and clinical response or adverse events would obtain multiple levels at several fixed doses of medication. We did not consistently note the time of the last drug dose, which could substantially influence exposure. This may have contributed to the considerable variation in drug concentration and also limited our ability to analyze these data using a population pharmacokinetics approach.[23,24] Our use of a 6-week measure of exposure to predict 12-week outcome assumes that 6-week exposure is representative of the overall exposure across the treatment period. Although levels obtained at 6 and 12 weeks were highly correlated, there certainly was evidence of variability. Participants were not genotyped for common genetic variations in cytochrome P450 enzymes, so we cannot determine to what extent the variability in drug exposure was because of how quickly participants metabolized

medications. Finally, we might have biased estimates of the relationships between drug level and both response and adverse events, as those who did not respond, who had serious adverse events, or who left the study before 6 weeks were much less likely to have had a drug level obtained.

Despite these limitations, this study is the first to examine the relationships between the drug concentration of SSRIs and SRNIs and the outcome in treatment-resistant depressed adolescents, and provides empirical support for the selective use of a dose increase for treatment nonresponders to either citalopram or fluoxetine.

In those treated with citalopram, higher plasma concentration assessed at 6 weeks predicted response at 12 weeks, with similar nonsignificant trend for those treated with fluoxetine. This finding has unclear predictive validity, insofar as there was no drug concentration cut point that sharply discriminated between responders and nonresponders. More specific effects were found among those who were nonresponders at 6 weeks and had a low drug concentration. For these youth, a dose increase in either citalopram or fluoxetine at 6 weeks was much more likely to result in response at 12 weeks if drug concentration moved from less than the GM at 6 weeks to equal to or greater than the GM by 12 weeks. In this sample, the GM for both citalopram and fluoxetine were lower than the concentrations estimated to achieve either 80% occupancy of the serotonin transporter in striatum or 80% serotonin reuptake inhibition, both of which are associated with clinical response.[16,25] Our finding that there was a greater likelihood of response in those participants whose levels of either citalopram or fluoxetine were greater than the GM is consistent with these observations.

We did not find a clear relationship between outcome and drug exposure for either paroxetine or venlafaxine. Because the GM of paroxetine and venlafaxine were higher than the minimum concentration reported by Meyer et al[16] to be associated with at 80% serotonin transporter binding, it is not surprising that further increases in dose and concentration were not beneficial. Although there is evidence in adults that higher doses of venlafaxine (ranging from 75 to 375 mg) result in greater efficacy, [10,26] our findings suggest that more is not necessarily better for depressed adolescents.

The results of this study provide preliminary evidence that clinical response to citalopram and fluoxetine in adolescent depression is related to exposure. Assessment of plasma levels may be particularly helpful for identifying youth who would benefit from a dose increase, namely, nonresponders to fluoxetine or citalopram who also have low drug concentration. Whereas it is true that current practice guidelines already recommend a dose increase of an SSRI if the patient does not respond to the initial dose of an antidepressant (1), these data suggest that an increase will be much more likely to be beneficial if current drug exposure is suboptimal. For those with adequate concentration, the clinician may do better to switch or augment than to increase the dose further. Future work that ties measures of drug concentration to biomarkers of response such as serotonin reuptake inhibition or changes in gene expression may help to identify a plasma concentration of fluoxetine or citalopram above which clinical response is likely. Such work could lead to empirically guided therapeutic monitoring strategies that personalize antidepressant dosing and substantially improve treatment response and clinical outcomes for depressed adolescents.

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Table 1

Plasma Concentrations for All Participants, Non-Responders, and Responders

	All Participants					Non-Responders					Responders				
	N	**M**	**SD**	**GM**	**90% CI**	**N**	**M**	**SD**	**GM**	**90% CI**	**N**	**M**	**SD**	**GM**	**90% CI**
Paroxetine	34	34.1	29.1	23.4	17.8–30.8	21	37.1	29.7	26.6	19.0–37.4	13	29.1	28.4	19.0	11.6–31.2
Citalopram	27	50.5	37.0	36.6	26.4–50.9	11	40.2	35.2	22.7	10.8–47.8	16	57.6	37.6	50.9	41.6–62.4
Fluoxetine	64	85.8	58.2	62.0	50.3–76.4	32	81.6	68.8	48.3	32.9–71.0	32	90.0	46.1	79.5	68.1–92.9
Norfluoxetine	64	96.4	44.9	79.6	67.4–93.9	32	88.8	50..3	65.5	48.3–88.8	32	104.0	38.1	96.6	85.5–109.2
Fluoxetine + Norfluoxetine	64	182.2	90.7	147.8	124.3–175.7	32	170.4	108.2	119.5	86.2–165.6	32	193.9	68.8	182.8	164.5–203.0
Venlafaxine	119	123.0	126.2	71.0	59.0–85.6	54	140.3	156.2	78.5	59.5–103.6	65	108.6	93.1	65.4	50.6–84.4
O-desmethylvenlafaxine	119	200.5	125.7	139.2	117.4–165.2	54	219.9	130.8	162.9	129.5–205.0	65	184.4	119.8	122.2	95.2–156.8
Venlafaxine + O-desmethylvenlafaxine	119	323.5	195.1	231.8	197.1–272.7	54	360.2	212.2	269.6	215.3–337.4	65	293.0	175.6	204.5	162.0–258.1

N=number of cases. M=arithmetic mean. SD=standard deviation. GM= geometric mean. CI=confidence interval. All data included. Zero-levels replaced with 4.0 ng/ml for paroxetine, venlafaxine and o-desmethylvenlafaxine, 1.5 ng/ml for citalopram, and 3.0 ng/ml for fluoxetine and norfluoxetine.

Table 2

Side Effects by Exposure at week-6 and Treatment Group[a]

	SSRI[b]				Venlafaxine			
Total No. Participants	**< GM[c]**		**≥ GM**		**< GM**		**≥ GM**	
	49		76		44		75	
	N	%	N	%	N	%	N	%
Appetite Disturbance	22	44.9	26	34.2	21	47.7	37	49.3
Cardiovascular[d]	19	38.8	27	35.5	14	31.8	46	61.3
Central Nervous System	38	77.6	57	75.0	36	81.8	64	85.3
Dermatology[e]	11	22.4	12	15.8	9	20.5	31	41.3
Dizziness Standing Up[f]	12	24.5	23	30.3	12	27.3	41	54.7
Gastrointestinal	35	71.4	43	56.6	29	65.9	53	70.7
Genito-Urinary	5	10.2	6	7.9	3	6.8	9	12.0
Headache	29	59.2	49	64.5	25	56.8	55	73.3
Irritability/Anger	27	55.1	46	60.5	26	59.1	52	69.3
Lethargy/Apathy	20	40.8	29	38.2	16	36.4	29	38.7
Mouth/Nose	24	49.0	33	43.4	23	52.3	36	48.0
Muskulo-Skeletal	15	30.6	23	30.3	14	31.8	28	37.3
Ocular	6	12.2	9	11.8	5	11.4	10	13.3
Sleep Disturbances	34	69.4	46	60.5	35	79.5	56	74.7

[a] Adverse effects reported by at least 5% of TORDIA participants on the Side Effects Form for Children and Adolescents. No statistically significant differences unless otherwise noted.

[b] Citalopram (n=27), fluoxetine (n=64), or paroxetine (n=34).

[c] GM = Geometric Mean.

[d] Venlafaxine: χ^2_1 =9.66, P=.002.

[e] Venlafaxine: χ^2_1 =5.42, P=.02.

[f] Venlafaxine: χ^2_1 =8.43, P=.004.

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