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Effects of Paroxetine and Sertraline on Low-Density Lipoprotein Cholesterol

An Observational Cohort Study

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Abstract

Background: Antidepressant use in US adults increased 3-fold from 2.5% in 1988–94 to 8.1% in 1999–2002, based on National Health and Nutrition Examination Surveys. As the use of antidepressants increases, a comprehensive understanding of the potential health risks that may be associated with their use becomes increasingly important.

Objective: This study evaluated the effects of paroxetine and sertraline on low-density lipoprotein cholesterol (LDL-C).

Study Design: An observational cohort study (1997–2004) of adults who had taken paroxetine or sertraline for at least 60 continuous days and had ≥2 LDL-C values measured during the study period, one while taking and one while not taking paroxetine or sertraline. A total of 13 634 LDL-C values clustered within 2682 patients were studied.

Methods: We conducted mixed model regression analyses to quantify the relationship between antidepressant use and LDL-C values.

Results: The number of days taking paroxetine ($\beta = 0.0045$; 95% CI 0.0018, 0.0073) and sertraline ($\beta = 0.0074$; 95% CI 0.0054, 0.0093) prior to the LDL-C test were related to higher LDL-C values, after accounting for age, sex, year LDL-C was tested, co-morbidity, depression and lipid medication. The number of days that had passed since exposure to paroxetine ($\beta = -0.0013$; 95% CI −0.0020, −0.00061) or sertraline ($\beta = -0.00093$; 95% CI −0.016, −0.00022) were related to lower LDL-C values. The significant interaction between exposure to an antidepressant and taking a lipid medication demonstrates that the increase in LDL-C values associated with antidepressant use is ameliorated among patients who were taking a lipid medication when LDL-C was measured.

Conclusion: Our study showed that long-term use of paroxetine or sertraline may have a measurable adverse impact on cardiovascular risk in adults. Clinical strategies should be used to address cardiovascular risk while maintaining effective treatment of major depression. In light of these findings, attention to LDL-C values should accompany antidepressant use.

Background

Antidepressant use in US adults increased 3-fold from 2.5% in 1988–94 to 8.1% in 1999–2002, based on National Health and Nutrition Examination Surveys.[1] Among enrollees with private health insurance from the largest US companies, 11% received antidepressant prescriptions in 2002.[2] Several factors drive the increased use of these medications. First, there is a great deal of emphasis on the need to systematically identify and treat depression, and to treat depression for longer periods of time than had previously been considered necessary. Second, the development of newer classes of antidepressant medications associated with fewer short-term adverse effects such as drowsiness, dry mouth and constipation has increased the acceptability of such medications, both for short- and long-term use. Third, new indications for the use of these classes of medications have been discovered to treat symptoms associated with a variety of chronic diseases, including peripheral neuropathy, fibromyalgia, pain and sleep disorders.[3-8] As the use of antidepressants increases, a comprehensive understanding of the potential health risks that may be associated with their use becomes increasingly important.

Recent research, including small clinical studies and post-marketing reports from the pharmaceutical companies, indicates there may be an association between antidepressant treatment and increased cardiovascular risk, including an increase in serum cholesterol levels.[9-18] The recent attention to the impact of long-term use of cyclo-oxygenase 2 (COX-2) inhibitors on cardiovascular risks,[19] and recent concerns that have emerged regarding the bone effects of antidepressants,[20-24] highlight the need for large community-based studies such as those that have assessed the impact of other commonly used medications on long-term health risks, for example, risks related to cardiovascular conditions.

The purpose of this study is to evaluate the effects of paroxetine and sertraline on low-density lipoprotein cholesterol (LDL-C). This is the first study that we are aware of that has an adequate sample size to fully quantify the relationship between exposure to antidepressant medication and LDL-C values among patients when they were and were not taking antidepressant medications. This study examines whether long-term use of paroxetine or sertraline could have an adverse impact on cardiovascular risk in adults.

The results of this study will enhance the ability of the healthcare community to assess risks for patients related to antidepressant use and improve care for these patients.

Methods

Study Site and Population

The study was conducted at HealthPartners Medical Group (HPMG), a large multi-specialty group in Minnesota, USA. During the years of the study, paroxetine and sertraline were the major antidepressant medications available on the HPMG formulary. The HealthPartners Institutional Review Board approved this study.

To be eligible for this study, an adult receiving care through HPMG had to meet the following criteria: (i) had continuous pharmacy coverage for the 12 months prior to an observed LDL-C value (allowing a 30-day gap); (ii) took paroxetine or sertraline between 1997 and 2004 for at least 60 continuous days; and (iii) had two or more LDL-C values available during this time period, one while taking and one while not taking paroxetine or sertraline. Exclusions were made for the following reasons: (i) those with modified Charlson Co-Morbidity Index scores >2 at the time of their first observed LDL-C value; or (ii) observations from men younger than 35 years, or women younger than 45 years, at the time of test.

Requiring pharmacy coverage in the year prior to the observed test value ensured that patient medication history was available so that time periods during which the patient was taking antidepressants could be accurately constructed and each observation correctly classified according to whether the patient was taking antidepressants at the time of the observation. The requirement that patients fill at least 60 continuous days of antidepressant prescriptions ensured minimum

exposure to these medications so that their hypothesized effect on cholesterol values could be observed. At least two LDL-C test values were observed from each patient, one while the patient was taking an antidepressant and one while the patient was not taking one; this ensured that intrapersonal changes in LDL-C values attributable to antidepressant use could be quantified. Finally, test values observed in patients with indications of significant co-morbid conditions (i.e. Charlson Co-Morbidity Index score >2) at the time of the first observed test value were excluded as alternative treatment recommendations could apply. The age inclusion criterion was based on the recommended ages at which routine cholesterol screening should be done: every 5 years for men over 35 years or women over 45 years.[25,26]

Outcome Variable

The unit of analysis was the observed LDL-C values clustered within patients during the study period (1997–2004). Application of the inclusion and exclusion criteria resulted in 13 634 LDL-C values from 2682 patients. During the entire study period, all LDL-C values were measured at a single centralized, accredited, clinical chemistry laboratory using a standard assay method. The calculation of LDL-C values from measured levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides was conducted using the Friedewald standard equation.[27] Less than 1% were directly measured LDL-C values, as was the custom in nearly all US clinical laboratories during the years of the study. LDL-C values were not calculated if triglycerides exceeded 400 mg/dL, or if the patient was fasting <12 hours before venipuncture.

LDL-C was chosen as our principal dependent variable because the relationship of triglycerides to cardiovascular risk is much weaker than the relationship of LDL-C or HDL-C to cardiovascular risk. With respect to HDL-C, it is difficult to achieve meaningful HDL-C improvement in most patients using available therapeutic choices with the exception of niacin, which is rarely used, and fibrates, which are relatively contraindicated in conjunction with statins due to concerns related to myositis. Therefore, in order to emphasize information that was of maximal practical use, we elected to focus on LDL-C.

Predictor Variables

A pair of variables was computed to quantify the patient's history of antidepressant use prior to each observed test value. These variables represent the amount of time, if any, the patient was taking an antidepressant prior to the test date, and the amount of time that had passed since the patient had taken an antidepressant. As a set, these covariates accounted for duration of exposure and time-lags between exposure to an antidepressant and observed test values.

Days having Taken Paroxetine or Sertraline

This variable represented exposure to paroxetine or sertraline immediately prior to the observed test value. If the patient was taking an antidepressant when the test value was observed, this was the number of days elapsed between the first medication fill for continuously used paroxetine or sertraline and the test date. If the patient was not taking an antidepressant when the test value was observed, this variable was coded zero (0).

Days since Last Taking Paroxetine or Sertraline

This variable represented the time-lag between last exposure to paroxetine or sertraline and the LDL-C test. If the patient was not taking paroxetine or sertraline when the test value was observed, this is the number of days that had elapsed since the end of the most recent supply for continuously used paroxetine (or sertraline). However, if a person was not taking paroxetine (or sertraline) at the time of the test and had not been observed taking the drug, then this is the number of days between the first date of their continuous enrolment (allowing a 30-day gap) that overlaps this particular test and the test date. This calculation thus represents the duration of time the patient was known to have not used the medication. If the patient was taking paroxetine or sertraline at the time of the test, this variable was coded zero (0).

Covariates

The following covariates were included in the analyses to control for factors that may vary across LDL-C observations within patients. Each covariate was calculated to refer to the date on which the test value was observed, except for sex.

Patient Sex

The sex of each patient was readily obtained from the electronic databases.

Patient Age

Patient age at the time each test was taken was included in the analysis to control for age-related changes in LDL-C.

Calendar Year of Observation

The calendar year during which the LDL-C test was taken was included to control for secular trends toward improvement on these measures over the course of the study period of 1997–2004.

Charlson Co-Morbidity Index Score

The Charlson Co-Morbidity Index score is a measure of co-morbidity that assigns points based on at least two ICD-9-CM[28] outpatient diagnosis codes recorded in the prior 12 months for a defined set of 19 serious diagnoses as described by Deyo et al.[29] and Rush et al.[30] The Charlson Co-Morbidity Index score for each patient wascategorized (0, 1, 2, 3+) to control for patient co-morbidity at the time of each LDL-C observation.

Depression Diagnosis

A diagnosis of depression is a potential confounder of the relationship between antidepressant medication use and LDL-C levels. We used ICD-9-CM codes for depression in the 6 months prior to the LDL-C test as a proxy of depression diagnosis.

Lipid Medication

An indicator variable denoted whether the patient was taking a lipid medication (e.g. statin, fibrate) at the time the LDL-C test value was observed.

Statistical Analysis

We conducted a series of mixed model regression analyses to quantify the relationship between antidepressant use, including duration of exposure, and LDL-C values. This approach readily accommodates the variable numbers of observations per patient and accounts for the within-person correlation among multiple LDL-C values. LDL-C values were nested within patient, an unspecified covariance structure was used, and restricted maximum likelihood estimation was implemented. Of primary interest were the parameters estimating the duration of exposure to an antidepressant, and the interaction between antidepressant exposure and lipid medication use. The analyses were conducted using SAS software (version 9.1) of the SAS System for Windows (SAS Institute, Inc., Cary, NC, USA).

Results

In total, 2682 people provided 13 634 LDL-C observations to the analyses. Patient characteristics measured at the time of the first observed LDL-C value during the study period (1997–2004) are shown in table I. Patients taking paroxetine or sertraline during the study period of 1997–2004 had initial LDL-C values from 30 to 341 mg/dL (mean 142.57 mg/dL, median 141 mg/dL). Over 82% of patients had an initial LDL-C value ≥100 mg/dL, 58% were ≥130 mg/dL and 29% were ≥160 mg/dL. Despite the high proportion of patients with high LDL-C values, only 20% were taking a lipid medication (e.g. statin, fibrate, other) at the time the initial LDL-C value was observed.

Characteristics of 13 634 LDL-C values observed during the study period, 1997–2004, are shown in table II. Over 38% of LDL-C tests performed during 1997–2004 were conducted in men, compared with 35% of the sample being men, indicating that men had a higher average number of LDL-C tests performed. Forty-nine

Table I. Characteristics of 2682 patients at the time of the first observed low-density lipoprotein cholesterol (LDL-C) value during the study period, 1997–2004

Characteristic	Value
Patient age (y) [mean ± SD]	54.7 ± 10.1
Male (%)	35.8
Year of first observed LDL-C value (%)	
1997	14.4
1998	26.6
1999	20.3
2000	16.5
2001	9.8
2002	8.1
2003	3.7
2004	0.6
Charlson Co-Morbidity Index score (%)	
0	64.4
1	26.3
2	9.3
Depression diagnosis in prior 6 months (%)	36.1
Taking a lipid medication at the time of the first LDL-C test (%)	19.6
No. of days patient taking paroxetine prior to test (mean ± SD)	79.4 ± 255.6
No. of days patient taking sertraline prior to test (mean ± SD)	172.8 ± 383.3
No. of days passed since patient last taken paroxetine (mean ± SD)	1177.7 ± 960.7
No. of days passed since patient last taken sertraline (mean ± SD)	821.8 ± 940.6
LDL-C values (mg/dL) [mean ± SD]	142.57 ± 37.25

percent of all LDL-C tests during 1997–2004 were performed while persons were taking a lipid medication, compared with 20% among the first tests. The percentage of depression diagnoses in the prior 6 months of all LDL-C tests performed during 1997–2004 was similar to the percentage among the first tests (35.6% vs 36.1%).

Table III displays the results of the analysis in which LDL-C values were predicted from exposure to antidepressants and patient covariates. The hypothesis that longer exposure to antidepressant medication was associated with higher LDL-C values was supported. Specifically, the number of days taking paroxetine ($\beta = 0.0045$; 95% CI 0.0018, 0.0073) and sertraline ($\beta = 0.0074$; 95% CI 0.0054, 0.0093) prior to the HDL-C test were both related to higher LDL-C values. Similarly, the number of days that had passed since exposure to paroxetine ($\beta = -0.0013$; 95% CI −0.0020, −0.00061) or sertraline ($\beta = -0.00093$; 95% CI −0.016, −0.00022) were related to lower LDL-C values. The significant interaction terms between exposure to antidepressant medication and taking a lipid medication demonstrate that the increase in LDL-C values associated with antidepressant use was ameliorated among patients who were taking a lipid medication when LDL-C was measured (figures 1 and 2). Older age, male sex and higher co-morbidity were related to lower LDL-C values. LDL-C values observed earlier in the study period were higher on average than those observed in the last study year of 2004, and a depression diagnosis within 6 months of the LDL-C test was related to higher LDL-C values.

Table II. Characteristics of 13 634 low-density lipoprotein cholesterol (LDL-C) values observed during the study period, 1997–2004

Characteristic	Value
Patient age at test (y) [mean ± SD]	57.7 ± 10.3
Male (%)	38.4
Year tested (%)	
1997	3.6
1998	10.1
1999	12.6
2000	15.2
2001	13.8
2002	15.8
2003	16.9
2004	12.0
Charlson Co-Morbidity Index score (%)	
0	53.1
1	28.2
2	11.7
3+	6.9
Depression diagnosis in prior 6 months (%)	35.6
Taking a lipid medication at the time of the LDL-C test (%)	49.3
No. of days patient taking paroxetine prior to LDL-C test (mean ± SD)	113.4 ± 340.8
No. of days patient taking sertraline prior to LDL-C test (mean ± SD)	195.3 ± 461.8
No. of days passed since patient last taken paroxetine (mean ± SD)	1494.2 ± 1257.5
No. of days passed since patient last taken sertraline (mean ± SD)	1050.4 ± 1176.0
LDL-C values (mg/dL) [mean ± SD]	128.38 ± 39.29

Table III. Predictors of low-density lipoprotein cholesterol (LDL-C) values during the study period, 1997–2004

Predictor	Parameter estimate (95% CI)
Intercept	152.12 (145.47, 158.78)
Days taking paroxetine prior to test	0.0045 (0.0018, 0.0073)
Days taking sertraline prior to test	0.0074 (0.0054, 0.0093)
Days passed since last taken paroxetine	–0.0013 (–0.0020, –0.00061)
Days passed since last taken sertraline	–0.00093 (–0.016, –0.00022)
Age at time of test (y)	–0.29 (–0.39, –0.18)
Male	–2.34 (–4.57, –0.11)
Year of LDL-C value	
1997	21.38 (18.24, 24.53)
1998	16.60 (14.30, 18.90)
1999	14.75 (12.65, 16.84)
2000	12.69 (10.75, 14.62)
2001	10.98 (9.09, 12.87)
2002	12.06 (10.28, 13.83)
2003	11.14 (9.44, 12.84)
2004	
Charlson Co-Morbidity Index score	
0	
1	–4.40 (–5.75, –3.04)
2	–7.86 (–9.75, –5.98)
3+	–7.65 (–10.02, –5.27)
Depression diagnosis in prior 6 months	3.31 (2.21, 4.41)
Taking a lipid medication at the time of the LDL-C test	–34.33 (–35.67, –32.99)
Interaction between no. of days patient taking paroxetine prior to test and taking a lipid medication	–0.0057 (–0.0090, –0.0024)
Interaction between no. of days patient taking sertraline prior to test and taking a lipid medication	–0.0065 (–0.0088, –0.0042)

Discussion

The purpose of this study was to evaluate the effects of antidepressant use on plasma lipoprotein profiles in a large and representative group of patients taking paroxetine or sertraline in a routine care setting. There was a total of 2682 people in our cohort who provided a total of 13 634 LDL-C observations. Patients taking paroxetine or sertraline during the study period (1997–2004) had a mean baseline LDL-C value of 142.57 mg/dL. Over 82% of patients had a baseline LDL-C value ≥100 mg/dL, 58% were ≥130 mg/dL and 29% were ≥160 mg/dL. While a given patient's cardiovascular risk is affected by many factors, including untreated depression, it is clear that for many patients the observed degree of LDL-C increase associated with the use of a selective serotonin reuptake inhibitor (SSRI) in our data could materially increase cardiovascular risk.[31]

Our results show that after accounting for age, sex, year tested, co-morbidity, diagnosis of depression and use of lipid medication, a longer period of time taking paroxetine or sertraline contributed to higher LDL-C values and a longer period of time not taking paroxetine or sertraline was related to lower LDL-C values. Although the magnitude of increase in LDL-C was relatively small per day, use of these medications for an extended period of time may be necessary for some patients to curtail major depression, and this extended use may therefore be associated with increased cardiovascular risk for these patients.

The potential association between antidepressant medications and an increase in serum cholesterol levels has been indicated in medical

compendiums as a possible occurrence in post-marketing reports.[9,13,14,16-18,32] In the prescribing information of Zoloft® (sertraline), it states that "Zoloft® therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%)."[17] Lara et al.[9] assessed the effects of 8 weeks of paroxetine administration (minimal therapeutic dosage of 20 mg/day) on plasma cholesterol and triglyceride levels in 19 healthy men after controlling for weight and diet. In the subjects who were nonsmokers and whose plasma concentrations of paroxetine indicated an unequivocal compliance to treatment (n = 16), paroxetine administration was found to induce an 11.5% increase in LDL-C. In 3 of the 16 subjects, the post-paroxetine treatment serum LDL-C levels were >2.59 mmol/L (100 mg/dL). Although the pharmacodynamic mechanisms underlying the increase in LDL-C in this study remain unclear, the increase appears to be shared by at least three medications, namely paroxetine, sertraline and venlafaxine.[33,34] Also needing further study is whether the paroxetine- or sertraline-induced increase in LDL-C is temporary or persistent. The persistence of such an increase would be particularly worrisome since lifetime pharmacological treatment with antidepressants is now the recommended treatment course following the recurrence of a major depressive disorder with complicating factors or multiple relapses.[7]

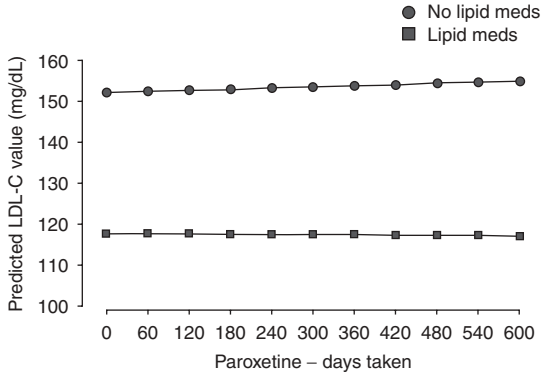

Fig. 1. Predicted low-density lipoprotein cholesterol (LDL-C) values based on the number of days the patient had taken paroxetine and whether the patient was taking a lipid medication. **Meds** = medications.

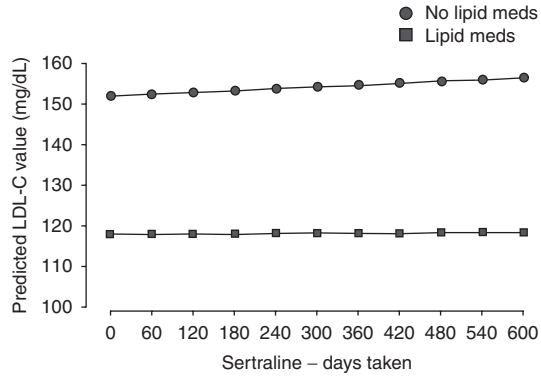

Fig. 2. Predicted low-density lipoprotein cholesterol (LDL-C) values based on the number of days the patient had taken sertraline and whether the patient was taking a lipid medication. **Meds** = medications.

Studies have also found a direct relationship between levels of LDL-C (or total cholesterol) and incident coronary heart disease (CHD) in men and women.[31,35-37] LDL-C levels also predict recurrent coronary events in patients with established CHD.[38,39] However, besides pre- and post-marketing trials conducted by antidepressant manufacturing companies, studies on the relationship between antidepressants and cholesterol have been limited to small sample size studies.[9-12,40,41] The current study used data from databases maintained by one large healthcare organization, allowing for the assembly of a virtually complete medical record for patients meeting the study inclusion criteria, and for exploration of relationships between antidepressant medication and cholesterol values over an extended period of time.

Our study shows that extensive long-term use of paroxetine or sertraline could have measurable adverse impacts on levels of cardiovascular risk in adults. While patients with major depression may require long-term use of these agents, current rates of antidepressant use now exceed estimates of the prevalence of major depression. This suggests that many patients who take these mediations may not have a diagnosis of major depression. In light of the findings of

this and other studies, use of antidepressants should be accompanied by attention to LDL-C values.

Our study has several limitations. First, current guidelines recommend cholesterol screening every 5 years for people over 35 (men) or 45 (women) years of age. Since study eligibility criteria required two or more LDL-C values in an 8-year study period, our study population may be slightly biased toward adults with higher LDL-C values. Second, the observational study design precludes causal inference, and it is possible that unmeasured confounders could have influenced the results. For example, we did not have body mass index data and it is possible that weight gain, which is sometimes associated with paroxetine use, might have mediated the elevated levels of LDL-C. However, while paroxetine may increase weight slightly,[42] sertraline is not associated with weight gain and, in some reports, is related to weight loss.[43] Because these two agents had similar LDL-C effects, it is unlikely that weight is a major mediator of the observed LDL-C impact. Third, since depression was derived from the ICD-9 codes in our study, it is possible that depression was under-reported.

There may be a number of effective clinical strategies to address the problem of cardiovascular risk for patients while maintaining effective treatment of major depression. Among these strategies would be: (i) initiating or titrating lipid or blood pressure medications early to reduce cardiovascular risk; (ii) modifying the pharmaceutical treatment of depression to lessen the adverse impact on cardiovascular risk; (iii) substituting psychotherapy or cognitive behavioural counselling for depression pharmacotherapy; or (iv) implementing adjunctive counselling in order to reduce doses of pharmaceutical agents for depression. The availability of these alternative clinical strategies meets the twin goals of both maintaining effective treatment of depression while at the same time not increasing cardiovascular risk. This study also underscores the need for further research in this area. Currently, antidepressants are seeing increasing use, but clinicians very rarely consider the potential adverse impacts of such agents on cardiovascular risk. However, documentation of such risk would provide a necessary incentive to modify depression treatment while still emphasizing the importance of effective control of depression.

Conclusion

Our study showed that long-term use of paroxetine or sertraline may have a measurable adverse impact on cardiovascular risk in adults. Clinical strategies should be used to address cardiovascular risk while maintaining effective treatment of major depression. In light of these findings, attention to LDL-C values should accompany antidepressant use.

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