Effect of Selective Serotonin Reuptake Inhibitors on the Risk of Fracture

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Background: Depression and osteoporotic fractures are common ailments among elderly persons. Selective serotonin reuptake inhibitors (SSRIs) are frequently used in the treatment of depression in this population, and the association between daily SSRI use and fragility fractures is unclear. Our objective was to examine the effect of daily SSRI use on the risk of incident clinical fragility fracture.

Methods: A population-based, randomly selected, prospective cohort study of 5008 community-dwelling adults 50 years and older, followed up over 5 years for incident fractures. Clinical fragility fractures were classified as minimal trauma fractures that were clinically reported and radiographically confirmed. The risk of fragility fracture associated with daily SSRI use was determined while controlling for relevant covariates.

Results: Daily SSRI use was reported by 137 subjects. After adjustment for many potential covariates, daily SSRI use was associated with substantially increased risk of incident clinical fragility fracture (hazard rate, 2.1; 95% confidence interval, 1.3-3.4). Daily SSRI use was also associated with increased odds of falling (odds ratio, 2.2; 95% confidence interval, 1.4-3.5), lower bone mineral density at the hip, and a trend toward lower bone mineral density at the spine. These effects were dose dependent and were similar for those who reported taking SSRIs at baseline and at 5 years' follow-up.

Conclusions: Daily SSRI use in adults 50 years and older remained associated with a 2-fold increased risk of clinical fragility fracture after adjustment for potential covariates. Depression and fragility fractures are common in this age group, and the elevated risk attributed to daily SSRI use may have important public health consequences.

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Depression is a common ailment among elderly persons, 1 affecting approximately 10% of primary care patients in the United States. 2,3 Selective serotonin reuptake inhibitors (SSRIs) are considered first-line therapy for the treatment of depressive symptoms among older adults because of their presumed favorable adverse effect profile. 4-6 The use of SSRIs is widespread; their combined sales in the United States exceeded $10.9 billion in 2004, representing a 32% increase since 2000. 7,8

The use of SSRIs has been associated with increased risk of fragility fracture 9-13; however, these studies used data from administrative databases and did not reliably control for many confounding variables that may affect the relationship between the use of these medications and fractures, such as falls, lifestyle behavior, symptoms of depression, and bone mineral density (BMD). A recent analysis of a cohort of postmenopausal women found that the use of tricyclic antidepressants (TCAs) was associated with increased risk of hip fracture, while controlling for many confounding variables, including BMD. 14 However, the same study 14 included few subjects taking SSRIs and was unable to demonstrate a relationship between SSRI use and fracture.

Recent research reveals a potentially important role for the serotonergic system in bone physiology. 15 Functional serotonin receptors and the serotonin transporter have been localized to osteoblasts and osteocytes, 16-19 and serotonin seems to modulate the skeletal effects of parathyroid hormone and mechanical stimulation. 16,17 A recent study 20 demonstrates that mice with a null mutation for the serotonin transporter had decreased skeletal mass and di-
minimized bone strength while growing mice treated with SSRIs had impaired bone gain.

Given the high prevalence of SSRI use and the frequent occurrence of fragility fractures in the elderly population, it is important to determine if daily SSRI use increases the risk of fracture. To estimate the effect of daily SSRI use on the risk of fragility fracture, we examined SSRI use within a large randomly selected population-based sample followed up prospectively for incident fragility fractures. We also examined the relationships between SSRI medication use, BMD, and falls.

STUDY DESIGN AND POPULATION

The Canadian Multicentre Osteoporosis Study (CaMos) has prospectively followed up a randomly selected population-based community cohort of noninstitutionalized men and women older than 25 years living within 50 km of 1 of 9 urban regional centers. Details of the CaMos cohort are reported elsewhere. Briefly, recruitment began in February 1996, and participants were interviewed by a trained interviewer to assess for osteoporosis and fracture-related risk factors. A second intensive interview was conducted 5 years after enrollment to reassess these risk factors. These follow-up interviews began in July 2000. This analysis was restricted to subjects 50 years and older at the 7 regional centers that obtained radiographic verification of all incident fractures. The study was approved by regional institutional ethics review boards, and participants provided written informed consent.

ASSESSMENT OF MEDICATION USE

Interviewers collected detailed drug information, including dosage, type of medication, route of delivery, and frequency of use. When interviews were conducted in participants’ homes, all contents of their medicine cabinets were reviewed. Most interviews were conducted outside of the participants’ homes, and for these interviews subjects were instructed to bring all of the contents of their medicine cabinets to the interview site. The SSRIs included in this study were those available on the market during the baseline interview, including citalopram hydrobromide, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, and sertraline hydrochloride. Medication use was assessed at 2 time points, with subjects reporting daily SSRI use at baseline and at year 5 considered recurrent users. All SSRI doses were standardized, such that the recommended starting dose for the treatment of depression for each SSRI was considered equivalent to 1 U (20 mg/d of citalopram, 20 mg/d of fluoxetine, 50 mg/d of fluvoxamine, 20 mg/d of paroxetine, and 50 mg/d of sertraline). For example, increasing the SSRI dose by 1 U would be equivalent to doubling the starting dose for depression. For patients taking higher doses of these medications, their dosage was considered a multiple of the starting dose. Persons were considered daily users of medications if they reported taking the medication every day.

BONE MINERAL DENSITY

Six of 7 centers measured BMD of the lumbar spine (L1-L4) and hip using Hologic QDR 1000, 2000, and 4500 (Hologic Inc, Waltham, Mass) dual-energy x-ray absorptiometry, while 1 center used a Lunar DPX (Lunar Corporation, Madison, Wis) densitometer. All BMD results were converted to a Hologic standard, using the method described by Genant et al. Each year, a European spine phantom was measured systematically at each site for standardization purposes. The BMD results reported are those at baseline.

ASCERTAINMENT OF FRACTURES

Subjects were mailed a questionnaire yearly until the end of year 5 of the study to ascertain if they had experienced a fracture in the previous year. Clinical fragility fractures were those that occurred owing to minimal trauma (eg, falling from bed, chair, or standing height). All reported clinical fragility fractures were confirmed radiographically by the study investigators.

OTHER MEASUREMENTS

Previous analyses demonstrate that the relationship between SSRI use and fractures may be substantially altered by confounding variables. Consequently, many covariates were considered as potential confounders. All covariates were assessed at the baseline interview. Demographic information (age, sex, education, and study center), weight, height, prior daily cigarette smoking for at least 6 months, alcohol intake during the past year, and physical activity (as assessed by recording the self-rated level of physical activity compared with peers at age 50 years, at age 30 years, during teenage years, and during childhood) were recorded. To assess for a history of falls, subjects were asked if they had fallen during the 30 days before the baseline interview. Prevalent self-reported minimal trauma fractures and prevalent x-ray–confirmed vertebral deformities were included as covariates. Calcium and vitamin D intake was assessed (supplementation and dietary) using a standardized calcium-specific and vitamin D–specific dietary questionnaire.

Comorbidities were assessed as a modified version of the Charlson comorbidity index and included breast cancer, prostate cancer, uterine cancer, dementia, hypertension, kidney disease, hepatic disease, rheumatoid arthritis, myocardial infarction, stroke and transient ischemic attack, types 1 and 2 diabetes mellitus, and chronic obstructive pulmonary disease. All comorbidities were based on subjects’ reports of diagnoses made by their treating physicians. This was done to ensure that the presence of these diseases was confirmed by a physician and was not based on the patient’s self-diagnosis. Other measures of comorbidity included general self-reported health (in answer to the question “In general, would you say your health is excellent, very good, good, fair or poor?”) and dementia as assessed by the Mini-Mental State Examination (MMSE) in subjects 65 years and older. For subjects younger than 65 years, an MMSE score of 30 was assumed, consistent with the age and education of the study population. Symptoms of depression were controlled for using the Mental Component Score (MCS) and the Mental Health Inventory 5 (MHI-5) scales of the Medical Outcomes Study 36-Item Short-Form Health Survey questionnaire. The MCS provides a validated measure of differences in mental health and exhibits a strong association with severity of depression among elderly persons, and the MHI-5 is a well-established measure for detecting depression. To improve the sensitivity of these measures for the detection of depressive symptoms, a participant was considered to have depressive symptoms if his or her score was less than 52 on the MHI-5 or less than 42 on the MCS.

Medication use considered as covariates included bisphosphonate use, daily use of antihypertensives, daily thiazide diuretic use, and ever use of daily oral, intravenous, intramuscular, or inhaled corticosteroids for 1 month or longer, as well as the following: menopausal estrogen therapy in women (measured as cumulative lifetime menopausal estrogen therapy), use of long-acting benzodiazepines (clorazepate dipotassium, di-
azepam, and flurazepam hydrochloride), use of anticonvulsants (Dilantin [phenytoin] and phenobarbitol), daily use of antipsychotics (chlorpromazine hydrochloride, clozapine, quetiapine fumarate, risperidone, thioridazine, thioridazine hydrochloride, and trifluoperazine hydrochloride), and daily use of TCAs (amitriptyline hydrochloride, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, imipramine hydrochloride, nortriptyline hydrochloride, and trimipramine maleate). These medication covariates were selected because of their associations with falls, fractures, depression, or low BMD.14,35-42

**STATISTICAL ANALYSIS**

Standard descriptive statistics were calculated. The effect of daily SSRI use on incident fragility fractures was examined using multivariate Cox proportional hazards regression analysis. The relationships between the dependent and independent variables were assessed for nonlinear trends, and proportional hazards assumptions were checked for the potential confounders previously listed. Model selection was carried out using the Bayesian information criterion.43 Because the main effect of interest was daily SSRI use, we assessed potential confounders by looking at the changes in the coefficient estimates for daily SSRI use across different plausible models, according to the Bayesian information criterion. Specifically, the effect of potentially confounding variables was considered across the 15 best models according to the Bayesian information criterion, and the coefficients for each variable were compared in all models. If a coefficient for a given model was stable across many models, we concluded that there was no confounding. If there was both no confounding and the variable itself seemed to have no effect on fractures, then this variable was removed from the model. Analyses were carried out using SAS (SAS Institute, Cary, NC) and R (version 2.3.0; The R Project for Statistical Computing, http://www.r-project.org).44

To assess the association of daily SSRI use with BMD and prevalent falls, linear and logistic regression modeling, respectively, was performed. Covariates used in both regression analyses included demographic and physical variables (age, sex, education, study center, and body mass index), comorbidities (self-reported general health, modified Charlson index, and MCS, MHI-5, and MMSE scores), habits (current cigarette use, physical activity, alcohol intake in the previous year, and calcium and vitamin D intake [from supplements and diet]), and medication use (TCAs, antipsychotics, anticonvulsants, benzodiazepines, antihypertensives, thiazide diuretics, and oral, intravenous, intramuscular, and inhaled corticosteroids). The difference in BMD associated with the use of SSRIs is expressed as percentage difference, derived from the regression coefficients using the formula 100% × β/mean BMD for nonusers at the baseline assessment.45

**RESULTS**

In total, 6005 subjects aged 50 years and older were enrolled at baseline from the 7 study centers that performed radiographic confirmation of incident fragility fractures. Nine hundred thirty-four subjects were excluded because they did not undergo baseline BMD testing, and 63 subjects had insufficient follow-up data. The resultant study population included complete baseline and follow-up data on 5008 subjects, of whom 137 (2.7%) were daily SSRI users and 609 (12.2%) reported depressive symptoms. This is similar to the prevalences recently reported among the Canadian general population and is similar to the prevalence of antidepressant use among the US general population.46,47 Daily SSRI users were more likely to be women, have depressive symptoms, report previous falls, and have lower BMD at the total hip. Daily SSRI users were also more likely to take long-acting benzodiazepines and anticonvulsants. Although daily SSRI users reported a higher prevalence of corticosteroid use, a substantial amount of corticosteroid use among this group was accounted for by inhaled corticosteroid use, which has not been clearly associated with fracture.48 Daily SSRI users and nonusers had high MMSE scores (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Daily SSRI Users (n = 137)</th>
<th>Nonusers (n = 4871)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>65.1 ± 8.7</td>
<td>65.7 ± 8.9</td>
</tr>
<tr>
<td>Female sex</td>
<td>114 (83.2)</td>
<td>3462 (71.1)</td>
</tr>
<tr>
<td>Body mass index, mean ± SD</td>
<td>28.2 ± 6.0</td>
<td>27.1 ± 4.7</td>
</tr>
<tr>
<td>Bone mineral density, mean ± SD/g/cm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip</td>
<td>0.86 ± 0.15</td>
<td>0.89 ± 0.16</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.95 ± 0.18</td>
<td>0.98 ± 0.18</td>
</tr>
<tr>
<td>Intake in previous 12 mo, mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium, mg/d</td>
<td>1112.9 ± 714.2</td>
<td>1025.0 ± 600.8</td>
</tr>
<tr>
<td>Total vitamin D, IU/d</td>
<td>204.5 ± 645.0</td>
<td>170.4 ± 573.1</td>
</tr>
<tr>
<td>Physical activity, mean ± SD</td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>Modified Charlson index, mean ± SD</td>
<td>0.9 ± 1.0</td>
<td>0.7 ± 0.9</td>
</tr>
<tr>
<td>Mini-Mental State Examination score, mean ± SD</td>
<td>29.1 ± 1.6</td>
<td>29.0 ± 1.8</td>
</tr>
<tr>
<td>Depressive symptoms, mean ± SD</td>
<td>54.0 ± 39.7</td>
<td>555.0 ± 11.4</td>
</tr>
<tr>
<td>No. of alcoholic beverages in previous 12 mo, mean ± SD</td>
<td>114.0 ± 225.7</td>
<td>157.4 ± 300.5</td>
</tr>
<tr>
<td>Ever cigarette smoker</td>
<td>80 (58.4)</td>
<td>2546 (52.3)</td>
</tr>
<tr>
<td>Prevalent falls in previous month</td>
<td>24 (17.5)</td>
<td>325 (6.7)</td>
</tr>
<tr>
<td>Prevalent vertebral deformity at baseline</td>
<td>10 (7.3)</td>
<td>377 (7.7)</td>
</tr>
<tr>
<td>Prevalent clinical fragility fracture at baseline</td>
<td>39 (28.5)</td>
<td>1262 (25.9)</td>
</tr>
</tbody>
</table>

Table 1. Baseline Selected Characteristics of the Study Population*

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

*Data are given as number (percentage) unless otherwise indicated.
†Calculated as weight in kilograms divided by height in meters squared.
DAILY SSRI USE AND INCIDENT FRAGILITY FRACTURES

Using univariate analysis, daily SSRI use was associated with substantially increased risk of fragility fracture (hazard rate [HR], 2.0; 95% confidence interval [CI], 1.3-3.1). After consideration of all listed covariates, the effect of daily SSRI use on incident clinical fragility fractures was adjusted for age, total hip BMD, modified Charlson index, prevalent vertebral deformity, prevalent fragility fractures at baseline, and cumulative lifetime estrogen use in women. Daily SSRI use was associated with increased risk of incident clinical fragility fracture (Table 2). The fractures that occurred among daily SSRI users tended to occur at clinically relevant sites (40% forearm, 21% ankle and foot, 13% hip, 13% rib, 9% femur, and 4% back). None of these fractures occurred at the skull, toes, or fingers. A dose effect of daily SSRI use on clinical fragility fractures was noted (Table 2). In the daily dose of SSRI, the risk of fragility fracture increased 1.5-fold (95% CI, 1.1-2.1). Daily SSRI users demonstrated decreased fracture-free survival compared with nonusers (Figure). Finally, recurrent daily SSRI users (those who reported taking SSRIs at baseline and at 5-year follow-up) had a multiple-adjusted increased risk of incident clinical fragility fracture similar to that of subjects who reported taking these medications at baseline (HR, 2.1; 95% CI, 1.1-4.0). In total, 162 subjects reported taking TCAs daily. Using the same covariates, daily TCA use was associated with increased risk of incident clinical fragility fracture (HR, 1.2; 95% CI, 0.7-2.2), but the wide 95% CI precludes any conclusions.

DAILY SSRI USE AND PREVALENT FALLS

At the baseline interview, daily SSRI use was associated with increased risk of falling. The multiple-adjusted odds ratio for a fall occurring during the month before the baseline interview associated with daily SSRI use was 2.2 (95% CI, 1.3-3.4). Daily SSRI use was associated with an increased risk of syncope. Using univariate analysis, daily SSRI use was associated with a 2-fold increased risk of incident clinical fragility fracture even after adjustment for many potential confounding variables. A dose effect of SSRIs on fractures was also observed. Subjects who used SSRIs at baseline and at follow-up had similar increased risks of fracture. Although daily SSRI use was associated with increased risk of falls and decreased BMD, it is unlikely that the effect of this class of drugs on fractures is explained entirely by these 2 mechanisms, as falls and BMD were controlled for in the estimation of the effect of daily SSRI use on fractures. Given the high prevalence of daily SSRI use among the general population, these results may have important public health sequelae.

In part, SSRIs may increase fracture risk because of their effect on bone physiology and on the risk of falling. Functional serotonin receptors and transporters have been localized to bone, while the administration of SSRIs decreases bone mass and strength in growing mice. In addition to the role of SSRIs in bone physiology, these drugs have been implicated in the cardiovascular system. Treatment of rat arterioles with SSRIs causes dilation of arterioles in skeletal muscle and cerebral vasculature and may lead to hypotension. A study of patients aged 65 years and older revealed that SSRI use is associated with increased risk of syncope. Our results suggest that BMD and falls may be affected adversely by daily SSRI use but that fracture rates remain elevated despite adjustment for these 2 risk factors, indi-

### Table 2. SSRI Use and Risk of Fragility Fracture

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate Adjusted Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily SSRI use</td>
<td>2.1 (1.3-3.4)</td>
</tr>
<tr>
<td>Daily dose of SSRI use</td>
<td>1.5 (1.1-2.1)</td>
</tr>
<tr>
<td>Recurrent daily SSRI use</td>
<td>2.1 (1.1-4.0)</td>
</tr>
</tbody>
</table>

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

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Daily SSRI use remained associated with a 2-fold increased risk of incident clinical fragility fracture even after adjustment for many potential confounding variables. A dose effect of SSRIs on fractures was also observed. Subjects who used SSRIs at baseline and at follow-up had similar increased risks of fracture. Although daily SSRI use was associated with increased risk of falls and decreased BMD, it is unlikely that the effect of this class of drugs on fractures is explained entirely by these 2 mechanisms, as falls and BMD were controlled for in the estimation of the effect of daily SSRI use on fractures. Given the high prevalence of daily SSRI use among the general population, these results may have important public health sequelae.

In part, SSRIs may increase fracture risk because of their effect on bone physiology and on the risk of falling. Functional serotonin receptors and transporters have been localized to bone, while the administration of SSRIs decreases bone mass and strength in growing mice. In addition to the role of SSRIs in bone physiology, these drugs have been implicated in the cardiovascular system. Treatment of rat arterioles with SSRIs causes dilation of arterioles in skeletal muscle and cerebral vasculature and may lead to hypotension. A study of patients aged 65 years and older revealed that SSRI use is associated with increased risk of syncope. Our results suggest that BMD and falls may be affected adversely by daily SSRI use but that fracture rates remain elevated despite adjustment for these 2 risk factors, indi-

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**Figure.** Fracture-free survival by selective serotonin reuptake inhibitor (SSRI) use.
cating that other pathways, such as impaired bone quality leading to reduced bone strength, may be of particular relevance. The MMSE scores in our study population were high (Table 1) compared with those in the general population. This reflects the fact that our study sampled a community-dwelling population and excluded nursing home residents. Our results demonstrate an important relationship between daily SSRI use and fractures among elderly persons, despite almost normal MMSE scores. It is possible that the relationship between daily SSRI use and fractures may be of greater magnitude in persons with dementia, as dementia is an independent risk factor for fracture. The use of corticosteroids is associated with increased risk of fracture. The magnitude of the relative risk associated with corticosteroid use in a large population-based study ranged from 1.33 to 2.6, depending on which fracture site was examined. A meta-analysis of several large cohort studies found that the risk ratio for osteoporotic fractures associated with corticosteroid use was 1.66 for subjects older than 50 years. Therefore, our results indicate that daily SSRI use is associated with a magnitude of fracture risk similar to that associated with corticosteroid use.

Previous analyses of the relationship between SSRI use and fractures used data from administrative databases and were limited in their inability to control for important confounding factors, such as falls, BMD, physical activity, and alcohol intake. Ensrud et al reported the effect of antidepressant medication use on fragility fractures in elderly women but were unable to discern the relationship between SSRI use and fragility fractures, likely because of an insufficient number of subjects. Most important, TCA use in that study was associated with increases in any hip fractures (HR, 1.83; 95% CI, 1.08-3.09). We found a similar multiple-adjusted relationship between TCA use and clinical fragility fractures (HR, 1.2; 95% CI, 0.7-2.2). In our study, there were 60% fewer TCA users, and it is likely that the smaller number of subjects taking TCAs in our study affects the uncertainty of our estimate. There are several potential weaknesses and strengths inherent to our study. First, the duration of daily use of SSRI use was unknown, precluding estimation of the effect of duration of use on fractures. However, the multiple-adjusted risk of incident clinical fracture was increased similarly in those subjects who reported daily SSRI use at baseline and at 5 years after follow-up (HR, 2.1; 95% CI, 1.1-4.0). It is possible, but unverifiable, that many of these subjects took SSRIs from baseline to year 5. Second, the subjects in this study were not evaluated by a psychiatrist for a diagnosis of depression but were assessed for depressive symptoms through the use of the MMSE, the MHI-5 scales of the Medical Outcomes Study 36-Item Short-Form Health Survey questionnaire. These are validated tools for the detection of depression. Third and most important, previous studies analyzing the relationship between depression and fractures that controlled for falls found no association between depression and fractures. Depressive symptoms were not associated with fragility fractures in our analysis in univariate or multiple-adjusted regression models. A strength of this study is the limited potential for ascertainment bias because incident fractures were radiographically confirmed. In addition, in separate analyses, daily SSRI users were not more likely to report adverse events, such as myocardial infarctions and cerebral vascular events. Finally, as in all observational studies, it is possible that daily SSRI use may be associated with an unknown confounder that was not controlled for. This large prospective study of persons aged 50 years and older provides evidence that daily SSRI use is associated with a 2-fold increased risk of clinical fragility fracture. Elderly persons are at increased risk of developing osteoporosis and depression. Daily SSRI use in this population to treat depression may increase the risk of subsequent fracture. These risks must be balanced against the benefits gained by the treatment of depression with SSRIs. In light of the high rate of SSRI use among the general population, and among elderly persons in particular, further studies that include controlled prospective trials are needed to confirm our findings.

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Errors in Text and Figure. In the Original Investigation by Liu et al titled “Prognostic Factors and Antibiotics in Vibrio vulnificus Septicemia,” published in the October 23 issue of the ARCHIVES (2006;166:2117-2123), errors appeared in both the text and Figure 2. In the Methods section of the abstract, the second and third sentences should have read as follows: “Patients were divided into 2 groups: those without HBNCLs (group 1) and those with HBNCLs (group 2). Patients were further divided into subgroups with fatalities (fatal subgroup) and those without fatalities (nonfatal subgroup).” In Figure 2B, the P value above the first 2 bars, for comparison of treatment outcomes using a third-generation cephalosporin plus tetracycline or its analogue vs other antibiotics, should have read “P<.001.” The ARCHIVES regrets the errors.