An Investigation of Water Lithium Concentrations and Rates of Violent Acts in 11 Texas Counties: Can an Association Be Easily Shown?

Sir: It has been suggested that lithium may be effective in the general treatment of impulsive aggression,[1] and quite a bit of literature has demonstrated an association of decreased suicidal behavior with lithium treatment.[2] Although there have been some negative studies,[3,4] several studies have suggested an association of lower lithium consumption with impulsive and aggressive behavior in humans. Dawson et al.[5] described an inverse correlation between the concentration of lithium in tap water and urine samples and state psychiatric hospital admissions and homicide rates in 24 Texas counties. Using Dawson and colleagues' lithium data, Schrauzer and Shrestha[6] reported a statistically significant inverse correlation between the concentration of lithium in drinking water and the incidence of suicide, homicide, and rape. However, their data on violent acts were from the years 1979–1987 and therefore represented the population in the counties 10 years after Dawson and colleagues' lithium data (1969) were collected. We designed a study to see if these findings could be easily and quickly replicated.

Method. Eleven counties (Bexar, Cameron, Dallas, El Paso, Hidalgo, Harris, Maverick, Tarrant, Travis, Val Verde, and Webb) were included in the study. Rates of violent acts (suicide, murder, rape, aggressive assault, and family violence) were calculated using data from the Texas Department of State Health Services Web site (2002)[7] and Texas Crime Report (2002).[8] Water utilities and other entities delivering drinking water to these communities were originally contacted to obtain data on the lithium concentrations. It was discovered that many of these entities did not keep records of lithium concentrations. Mean dissolved lithium concentrations were calculated using data from the Texas Water Development Board Groundwater and Surface Water databases for the years 1992 to 2002.[9] Numbers of samples and sample sites and lithium concentration values were collected.

Statistical analyses were planned to examine (1) correlations between lithium concentration and various measures of violent crime rate using year as the unit of analysis and (2) the associated univariate statistics (mean and standard deviation values).

Results. Counties sampled differed greatly in multiple demographic characteristics. Counties ranged from relatively small rural communities to major metropolitan areas, with populations ranging from 46,011 (Val Verde) to 3,540,965 (Harris). Economic parameters also differed greatly between counties, with per capita personal income ranging from $12,430 (Maverick) to $36,825 (Harris), percentage of the population below the poverty level ranging from 11.4% (Tarrant) to 30.6% (Cameron), and unemployment rates ranging from 5.3 (Bexar) to 24.7 (Maverick). The racial composition of counties was also quite different, with percentages of the 3 major ethnic groups as follows: Anglo, 3.5% (Maverick) to 60.4% (Tarrant); Black, < 1% (Cameron, Hidalgo, Maverick, Webb) to 20.4% (Dallas); and Hispanic, 21.5% (Tarrant) to 95.1% (Maverick).

Wide variability by county was noted in various aspects of water sampling and reported lithium values. First, the number of sites sampled per county varied from 0 (Hidalgo, Maverick) to 6 (Bexar) for surface water and from 1 (Cameron, Harris) to 4 (Webb) for groundwater. A great deal of variability was also noted in the number of water samples tested per county. For surface water, this number ranged from 0 (Hidalgo, Maverick) to 221 (Val Verde), and for groundwater, from 7 (Maverick) to 307 (Bexar). Mean lithium concentrations ranged from 13.6 µg/L to 116.6 µg/L. Wide variability was also found in the lithium values reported, with groundwater values ranging from 2 µg/L (Val Verde) to 749.6 µg/L (Bexar) and surface water values from 4 µg/L (4 counties) to 230 µg/L (El Paso). A great amount of variability was also noted in samples collected within the same county. For instance, Bexar County alone reported lithium values ranging from 4 µg/L to 580 µg/L for surface water and 2.1 µg/L to 941 µg/L for groundwater.

Wide variability by county was also noted for rates of violent acts, which ranged from 2.1 to 13.1 for suicide, from 2.4 to 10.6 for murder, from 0.0 to 42.1 for rape, from 119.5 to 530.8 for aggressive assault, and from 795.3 to 3853.4 for family violence.

Mean lithium concentrations and rates of violent acts were standardized by calculating z scores. Pearson correlation coefficient was calculated to assess correlation between these variables across all counties and was found to be nonsignificant ($r = -0.35$).

In the opinion of the authors, the association between water lithium concentrations and violent acts cannot be easily assessed. Several factors make the interpretation of these data extremely difficult. This study highlights the difficulties of conducting geomedical research with many possibilities for confounding present. A great amount of variability was noted between counties in a number of characteristics. These included variability in economic factors as well as in population size and racial composition. Other factors such as the location of the counties might also have a bearing on the rates of violent acts. For instance, some counties are located on the U.S.-Mexico border, while others are not.

Testing of water supplies for lithium concentrations is not standardized in Texas, which leads, in part, to the wide variability noted in the data. A shortcoming of the present study is that we included lithium concentrations from all water sources as opposed to water sources used for public water supply. Even though many of these water supplies are sources for drinking water, this information is difficult to assess because different water sources provide varying percentages of the water used for public consumption during different times of year. Future studies should include only water supplies used for public consumption.

A prospective study such as that conducted by Dawson et al. in 1969 would be necessary to assess the question. Random sampling would be needed to account for possible confounding factors. Variability in water consumption and dose relationships of lithium must be accounted for if causal inferences are to be made. Even factors that are seemingly trivial, such as bottled water consumption, would need to be addressed. Higher concentration of lithium in drinking water may eventually be shown to be associated with a decrease in violent acts, but this will not prove to be an easy endeavor.

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Robert Gonzalez, M.D.
Ira Bernstein, Ph.D.
Trisha Suppes, M.D., Ph.D.
Department of Psychiatry
University of Texas Southwestern Medical Center
Dallas, Texas

Shared Decision Making in Schizophrenia Treatment

Sir: I read with great interest the article by Hamann et al.[1] in the July 2007 issue of the *Journal*. First, I applaud the authors' focused effort[2,3] to answer the thorny question about whether and how patients with schizophrenia can be engaged in therapeutic decisions and what the consequences of this inclusion might be.

My first comment refers to some of the numbers reported in the article. The authors report a sample size of 107 subjects at baseline, 86 patients at the 6-month follow-up, and 71 patients at the 18-month follow-up. They also report that 16 subjects, or 22% of the study subjects, were rehospitalized within 6 months from discharge and "another" 33 (42%), between 6 and 18 months after discharge. If one is to follow the logical implications of the "another" specifier and add these numbers (i.e., 16 + 33), the result is 49 and not 39 (as reported). Additionally, it is not clear how the number of subjects rehospitalized at 6 months (16) translates to 22% and, similarly, how the number of patients rehospitalized between 6 and 18 months translates to 42%. To illustrate, 16 of the original sample of 107 is 15%, and 16 of the sample of 86 at 6-month follow-up is 19%. Neither number is 22%.

Second, I would like to comment on 2 of the study's apparently paradoxical findings: the association of both a higher desire of the patients for autonomy and better knowledge of the discharge plan with higher future rehospitalization rates. With regard to the first, the authors report that the patients expressing higher participation preferences were also shown to be less satisfied with care and involvement with medical decisions and propose that a mismatch between the patients' (high) expectations and their doctors' performance might result in dissatisfaction with the doctors' services and future noncompliance. The authors only briefly comment on the paradoxical aspect of one of their most interesting findings, i.e., that better knowledge at discharge seemed to predict poorer outcomes. They suggest that this counterintuitive finding might result from perceived inadequacies of the limited psychoeducational approach used in the study. As interesting as such explanations might be, as they are not data based, they remain mostly speculative.

As previously discussed,[4] there is an alternative explanation for these paradoxical findings. It is likely that patients with prominent paranoia would show a higher desire for autonomy, less satisfaction with care and medical decisions, and better knowledge at discharge (as it can be anticipated that they would want to be fully informed at all times about the different aspects of their treatment) as well as an increased rate of noncompliance (due to lack of trust in their providers or the recommended treatments). These factors, reflecting a unique pathology, would have the cumulative effect of a higher risk for future relapse and rehospitalization. Our alternative has the following advantages: (1) it is a more parsimonious explanation (proposing a single cause for apparent heterogeneous and paradoxical findings) and (2) it can easily be verified against data that have already been collected and as such is less speculative than those proposed by the authors. A simple analysis of the Positive and Negative Syndrome Scale subscores for delusions and paranoia in the patients showing paradoxical prediction results would easily provide evidence for or against the proposed hypothesis.

Dr. Preda reports no financial affiliation or other relationship relevant to the subject of this letter.

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Adrian Preda, M.D.
Department of Psychiatry and Human Behavior
UC Irvine Medical Center
Orange, California

Dr. Hamann and Colleagues Reply

Sir: First, we would like to address Dr. Preda's questions regarding numbers and percentages. As reported in our article,[1] 16 patients were rehospitalized within 6 months after discharge and 33 were rehospitalized between 6 and 18 months after discharge. Some of the latter had already been rehospitalized in the earlier period, reducing the sum to 39 patients who had been hospitalized at least once within 18 months after discharge.

Second, we reanalyzed our data as suggested by Dr. Preda to study whether patients with prominent paranoia would show a higher desire for autonomy, less satisfaction with care, better knowledge at discharge, and an increased rate of noncompliance. We therefore calculated the correlations of the Positive and Negative Syndrome Scale (PANSS) items for delusions and paranoia as well as the PANSS subscore for positive symptoms

with the variables of interest. As reported earlier,[2] there was no association between psychopathology and patients' desire for autonomy.

Thus, counter to Dr. Preda's suggestion, patients with more expressed delusions or paranoia did not show higher participation preferences. Furthermore, patients showing more expressed delusions or paranoia knew less about their disease—contrary to the hypothesis of Dr. Preda. However, there was an association between more expressed paranoid symptoms/positive symptoms at discharge and poorer satisfaction with care as well as with poorer compliance at 18 months, but not at 6 months.

Thus, the hypothesis that paranoia/distrust leads to a higher desire for autonomy and to better knowledge is not supported by our data. The association between paranoia/distrust and poor satisfaction/poor compliance might be explained by the fact that patients who still suffer from core symptoms of schizophrenia (paranoia) at discharge simply cannot be satisfied with their treatment (which in their view does not solve, e.g., the problem of being persecuted) and are unlikely to be compliant with antipsychotic medication.

The relationship between poor symptom control and poor compliance has also been demonstrated earlier (see Fenton et al.[3] for example) and does not contradict the results reported in our study. In this context, we recall that in our study we performed a multivariate analysis, and the associations reported (participation interests × rehospitalization) were found while controlling for PANSS scores.

Dr. Hamann has received honoraria and/or research support from Janssen-Cilag, Sanofi-Aventis, AstraZeneca, Eli Lilly, Boehringer, and Bristol-Myers Squibb. Dr. Leucht has received honoraria and/or research support from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Janssen-Cilag, Johnson & Johnson, and Lundbeck. Dr. Kissling has received honoraria from Janssen-Cilag, Sanofi-Aventis, Johnson & Johnson, Pfizer, Bristol-Myers Squibb, AstraZeneca, Lundbeck, Novartis, and Eli Lilly.

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Johannes Hamann, M.D.
Stefan Leucht, M.D.
Werner Kissling, M.D.
Department of Psychiatry
Technische Universität München
Munich, Germany

Asymptomatic QTc Prolongation During Coadministration of Aripiprazole and Haloperidol

Sir: Several non-antiarrhythmic drugs, including antipsychotic agents, have been shown to prolong cardiac repolarization, predisposing to torsades de pointes ventricular tachycardia and sudden cardiac death.[1] However, it is known that several risk factors may prolong QT interval, even in patients with an apparently normal baseline electrocardiogram (ECG).[2] Psychoactive polytherapy has to be included in these risk factors due to pharmacokinetic and pharmacodynamic interactions.[3] Therefore, QT prolongation represents a marker of torsades de pointes and sudden cardiac death risk and can be considered a warning to modify pharmacologic treatment.

Case report. Ms. A, a 43-year-old woman, was referred as an outpatient with schizophrenia to our Neuropsychiatric Department in April 1996. Six months earlier, she had been started on aripiprazole therapy (15 mg daily). The baseline ECG showed a normal QT interval (corrected QT [QTc] = 417 milliseconds). Because of psychotic symptom recurrence, aripiprazole therapy was increased to 30 mg daily, for 3 months, without subsequent significant QT variation (QTc = 415 milliseconds). Since the increased dose of aripiprazole was inefficacious, haloperidol (5 mg daily) was added. After a week of combination therapy, the ECG showed a prolonged QTc interval of 492 milliseconds, without cardiologic symptoms. After haloperidol withdrawal, a gradual reduction of QT interval was observed, 450 milliseconds after a week and 428 milliseconds after 2 weeks.

QT interval is defined as the period from the onset of the QRS complex to the end of the T wave and represents the time of ventricular depolarization and repolarization. Since QT interval is reduced with the increasing of cardiac frequency, QT measurement is to be corrected by cardiac frequency value (corrected QT). In this case, QT intervals were measured manually with the precision of 10 milliseconds, corrected according to Bazett's formula, and rounded to the nearest 10 milliseconds (consistent with present clinical practice). QTc intervals of 470 milliseconds in females and 450 milliseconds in males are considered borderline; QTc intervals above these values are considered pathologic.[2]

Aripiprazole, a quinolinone derivative, is an atypical antipsychotic drug that has a high affinity for dopamine D_2 and D_3 receptors and serotonin-1A ($5\text{-}HT_{1A}$), $5\text{-}HT_{2A}$, and $5\text{-}HT_{2B}$ receptors and is indicated for the treatment of adult patients with schizophrenia.[4,5] Aripiprazole 10 or 15 mg once daily is effective and well tolerated. Current data generally indicate that aripiprazole has a beneficial profile in terms of QT interval prolongation. Aripiprazole is rapidly absorbed after oral administration. The mean time to peak plasma concentration is 3 hours following multiple-dose administration of aripiprazole 10 or 15 mg, and the absolute oral bioavailability of the drug is 87%. Steady-state plasma drug concentrations are achieved by 14 days; however, the drug appears to accumulate over this period, since mean peak plasma concentration and mean area under the plasma concentration–time curve values of 10 or 15 mg/day are 4-fold greater on day 14 than on day 1. This accumulation may be expected since the mean elimination half-life of a single dose of aripiprazole is about 75 hours.[6]

Aripiprazole has extensive extravascular distribution, and more than 99% of aripiprazole and dehydro-aripiprazole (the main active metabolite of aripiprazole) is bound to plasma proteins. Elimination of the drug is primarily hepatic; the cytochrome P450 3A4 (CYP3A4) and CYP2D6 enzyme systems transform aripiprazole to dehydro-aripiprazole, with the latter enzyme system subject to genetic polymorphism.[7,8] Thus, dosage adjustment of aripiprazole is necessary when it is coadministered with CYP3A4 and CYP2D6 inhibitors (since aripiprazole concentration is increased). Although aripiprazole has only been directly compared with haloperidol in treatment-responsive patients, to date few data are reported in the literature on combined administration of the 2 drugs.[9,10] Even if haloperidol is considered by psychiatrists as safe without significant cardiotoxic effects, it may induce a proarrythmic effect.[11]

Haloperidol was introduced in 1958, and to date, this antipsychotic drug is frequently prescribed not only by psychiatrists but also in medicine and surgery to induce sedation. Haloperidol has been observed to predispose to QT prolongation and torsades de pointes,[12–14] even though recent studies demonstrated its therapeutic safety.[15,16]

Haloperidol and its reduced form are substrates of CYP3A4 and inhibitors of CYP2D6, thus pharmacokinetic interactions may occur between haloperidol and other drugs given concomitantly, e.g., aripiprazole.[17,18]

Cytochrome P450 drug oxidases play a pivotal role in the elimination of antipsychotic agents and therefore influence the toxicity and efficacy of these drugs. Factors that affect CYP function and expression have a major impact on treatment outcomes with antipsychotic agents. In particular, aspects of CYP pharmacogenetics and the processes of CYP induction and inhibition all influence in vivo rates of drug elimination.[7,8] We suppose a potential pharmacokinetic interaction between aripiprazole and haloperidol because of the same metabolic pathway by CYP3A4 and CYP2D6.

In this case, we did not evaluate plasma drug concentrations, and for this reason our explanation for the observed QTc prolongation is clearly speculative.

Nevertheless, we suggest caution when aripiprazole is used with any potential 3A4 substrate or inhibitor. Our case highlights a potential drug interaction between aripiprazole and haloperidol leading to QTc prolongation during the management of patients with schizophrenia. One of the most effective preventive measures in groups of patients at risk remains QT interval monitoring by ECG screening.

Further studies are needed to define a possible pharmacodynamic or pharmacokinetic interaction between aripiprazole and haloperidol.

Drs. Leo, Razzini, Di Lorenzo, Bianchi, Tesauro, Zanasi, Siracusano, and Romeo report no financial or other relationships relevant to the subject of this letter.

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Roberto Leo, M.D., F.A.C.P.
Cinzia Razzini, M.D.
Department of Internal Medicine
Division of Cardiology
Giorgio Di Lorenzo, M.D.
Francesco Bianchi, M.D.
Department of Neuroscience
Division of Psychiatry
Manfredi Tesauro, M.D.
Department of Internal Medicine
Division of Cardiology
Marco Zanasi, M.D.
Alberto Siracusano, M.D.
Department of Neuroscience
Division of Psychiatry
Francesco Romeo, M.D., F.A.C.C., F.E.S.C.
Department of Internal Medicine
Division of Cardiology
Tor Vergata University
Rome, Italy

Is Clozapine Safe in Patients With Preexisting Epilepsy? A Report of 2 Cases

Sir: Clozapine is associated with seizures in 2% to 3% of patients who receive it.[1,2] This risk increases when patients have preexisting neurologic abnormalities.[2] Langosch and Trimble have described the use of clozapine in the treatment of psychosis in patients with epilepsy.[3] Whereas it remains controversial whether clozapine induces or reduces tardive dyskinesia, an open-label study favors its use in this condition.[4] Valproic acid and the newer antiepileptic drugs may be safely used with clozapine.[5,6] We administered clozapine in 2 patients with history of previous epilepsy.

Case 1. Mr. A, a 23-year-old man, was admitted to the psychiatry unit in March 2006 with an 8-month history of DSM-IV psychotic disorder due to a medical condition (epilepsy). He had complex partial seizures with secondary generalization, the first episode in 1997 and the second in 2000. The electroen-

cephalogram (EEG) showed patterns of generalized seizure. He developed postictal psychosis following the first episode of seizure. This was successfully treated with haloperidol, which was ceased later. He was taking carbamazepine at the time of admission. While the postictal psychosis responded to haloperidol, his current psychotic symptoms remained unchanged after the administration of an adequate dosage of haloperidol, risperidone, and olanzapine for adequate duration.

We decided to start clozapine in view of the refractory nature of Mr. A's psychosis. We obtained informed consent from his caretaker. Baseline EEG showed occasional seizure focus. Carbamazepine was cross-tapered with sodium valproate and finally ceased 1 month prior to the administration of clozapine because of the added risk of agranulocytosis with the combination of both drugs.[7,8] Clozapine was then started at a daily dose of 25 mg and was titrated up to 400 mg. EEG that was recorded when the daily dose reached 400 mg revealed no new changes. The psychotic symptoms gradually resolved over a period of 6 months.

As noted at 1-year follow-up, there was no incidence of seizure while he was taking clozapine as maintenance treatment.

Case 2. Mr. B, a 22-year-old man, was admitted in May 2006 with a 10-year history of abnormal behavior associated with severe mental retardation and 3-year history of tardive dyskinesia. He had recurrent generalized tonic-clonic seizures that started when he was 3 years of age. The last episode was 1 week after admission. He had received carbamazepine ever since the first incidence of seizure. Haloperidol and lithium were administered for 10 years to treat his aggression.

We decided to start clozapine owing to Mr. B's abnormal behavior and severe tardive dyskinesia. We obtained informed consent from his caretaker. Baseline EEG showed multiple foci. As with Mr. A, carbamazepine was cross-tapered with sodium valproate and finally ceased 1 month prior to the administration of clozapine, which was started at a daily dose of 25 mg and then titrated up to 500 mg. EEG that was recorded when the daily dose reached 400 mg revealed no new changes. As was the case with Mr. A, Mr. B's psychotic symptoms gradually resolved over a period of 6 months; in addition, his behavioral problems as well as his dyskinetic movements significantly subsided within 3 months of treatment with clozapine.

One-year follow-up revealed that there was no incidence of seizure while Mr. B was taking clozapine as maintenance treatment.

Given that clozapine appears to be safe with certain anticonvulsants, epilepsy need not preclude the use of this revolutionary drug whenever it is clinically appropriate. A 6-month trial may be needed to establish the efficacy of clozapine in patients with epilepsy; however, the dose should be kept as low as necessary.

The authors report no financial affiliation or other relationship relevant to the subject of this letter.

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James T. Antony, M.D., M.R.C.Psych.
Department of Psychiatry
Jubilee Mission Medical College
Thrissur, Kerala, India
Alby Elias, M.D.
Department of Psychiatry
Northern Sydney and Central Coast Health Services
Newcastle, Australia
Fiju Chacko, M.D., D.M.
Department of Neurology
Jubilee Mission Medical College
Thrissur, Kerala, India
Biju Rajan, M.R.C.Psych.
Department of Psychiatry
Northern Sydney and Central Coast Health Services
Newcastle, Australia

Corrections

In the article "Relevance of Family History of Suicide in the Long-Term Outcome of Bipolar Disorders" by Soledad Romero, M.D., and colleagues in the October 2007 issue (J Clin Psychiatry 2007;68:1517–1521), the coauthor's family name should have been spelled *Pacchiarotti* in the byline and in 2 footnotes to the article on page 1517. The online version of the article has been corrected.

In the article "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Methylphenidate Transdermal System in Pediatric Patients With Attention-Deficit/Hyperactivity Disorder" by Robert L. Findling, M.D., and colleagues in the January 2008 issue (J Clin Psychiatry 2008; 69:149–159), the word *maximum* should be inserted on page 155 in the right column, 5 lines above the page foot, to read as follows: "The maximum mean increase from baseline in systolic and diastolic blood pressures was 1.3 mm Hg and 1.6 mm Hg, respectively, for MTS and 1.6 mm Hg and 2.7 mm Hg, respectively, for OROS methylphenidate." The online version of the article has been corrected.