Is Second-Generation Antipsychotic–Induced Hyperprolactinemia Due to Biologically Active Prolactin or to Biologically Inactive Macroprolactin? Results From a Prospective Study

Sir: Hyperprolactinemia is of particular concern with antipsychotic medication, as symptoms associated with high prolactin levels, e.g., sexual dysfunction, can have a negative impact on the patient's adherence to treatment, and has significant implications for the short-term and long-term health of patients. In general, second-generation antipsychotics (SGAs) produce lower increases in prolactin levels than first-generation antipsychotics due to the differences in these drugs' binding affinity for the dopamine D_2 receptor.[1,2] Particularly, olanzapine, quetiapine, and clozapine have been shown to produce no significant or sustained increase in prolactin. Conversely, SGAs that have been associated with increases in prolactin levels are amisulpride, zotepine, and risperidone.[3–6]

Besides monomeric prolactin, which accounts for approximately 85% of total prolactin in normal sera, higher-molecular-weight variants of prolactin are known. Macroprolactin, which in the majority of cases consists of antigen-antibody complexes of monomeric prolactin and immunoglobulin G,[7] contributes less than 1% to circulating prolactin levels.[8] However, in some patients with supraphysiologic prolactin levels, macroprolactin was demonstrated to be the predominant form without eliciting the classical signs and symptoms of the hyperprolactinemic syndrome.[7,9,10]

Commonly used immunoassays for prolactin measurement fail to differentiate between biologically active monomeric prolactin and macroprolactin because of the assays' variable degree of reactivity with macroprolactin.[11,12] Conservative estimates suggest that the presence of macroprolactin leads to misdiagnosis in as many as 10% of all reported instances of biochemical hyperprolactinemia.[13]

In this prospective study, we investigated whether SGA treatment–induced hyperprolactinemia might be the result of an increase in macroprolactin levels in order to allow for better differentiation between symptoms caused by the antipsychotic agent and those that are disease related.

Method. In the present study, conducted from November 1999 through July 2005, patients aged 18 to 65 years and diagnosed with schizophrenic disorder according to the *International Classification of Diseases*, Tenth Revision (ICD-10) were recruited from the Schizophrenia Services Outpatient Clinics, Department of Psychiatry, Innsbruck Medical University. All patients gave written informed consent to participate in this study, which was approved by the Ethics Committee of Innsbruck Medical University.

Twenty-nine patients were included and had a washout period of 3 days if they were pretreated with oral medication and 1 injection interval if they were pretreated with depot medication. After the washout period, patients were assigned to monotherapy with olanzapine (N = 7), clozapine (N = 6), risperidone (N = 6), amisulpride (N = 7), or ziprasidone (N = 3). All SGAs were dosed according to standard dosage procedures.

Serum levels of prolactin and macroprolactin were measured both before treatment and at 28 days after the start of treatment. Blood was drawn in the morning after an overnight fast, and plasma samples were stored at –80°C until assayed. Prolactin concentrations were determined by a solid-phase, 2-site chemiluminescent immunometric assay using an Immulite 2000 analyzer (DPC, Los Angeles, Calif.). After the initial measurement of prolactin concentration, 250 µL of serum, mixed with an equal volume of 250-g/L polyethylene glycol (PEG) 8000 (Sigma-Aldrich, St. Louis, Mo.) in phosphate-buffered saline (pH = 7.4), was incubated for 10 minutes at room temperature. The suspension was clarified by centrifugation at 14,000g for 5 minutes before quantification of macroprolactin in the supernatant by the same immunometric assay as used before.

Normal prolactin values were 2 to 20 µg/L in men and 5 to 25 µg/L in women. After PEG pretreatment, a prolactin recovery rate ranging from 76% to 144% was indicative of mainly monomeric prolactin in the sample. While a recovery rate ranging from 54% to 76% suggested increased macroprolactin, a recovery rate of less than 55% was considered to be consistent with macroprolactinemia. In addition, percentages were converted to absolute values to rule out the simultaneous occurrence of an absolute elevation of monomeric prolactin, thereby reducing the risk of misclassification. Because of the nonparametric distribution of data, the Wilcoxon signed rank test was applied within groups for prospective comparisons as well as for comparisons between prolactin concentrations before and after PEG precipitation.

Results. The median age of the study population (19 men, 10 women) was 34 years, ranging from 18 to 57 years. Results of prolactin measurements at baseline and after 28 days are summarized in Table 1. No significant differences in prolactin levels before and after PEG precipitation were observed in any of the treatment groups (Table 1). Hyperprolactinemic samples from patients treated with olanzapine, clozapine, and amisulpride contained exclusively monomeric prolactin both at baseline and after 28 days. In the risperidone group, 1 patient showed an increased macroprolactin concentration at baseline, which returned to a lower level (but was still suggestive of macroprolactinemia) after 28 days. In 1 ziprasidone-treated patient with hyperprolactinemia at study entry, macroprolactin concentration remained elevated after 4 weeks.

The results from this prospective study confirm the high propensity of amisulpride and risperidone for causing hyperprolactinemia,[2,3] as treatment with amisulpride and risperidone resulted in a nearly 3-fold increase in prolactin concentrations. Both olanzapine and clozapine had no substantial impact on serum prolactin levels during treatment and even led to lower prolactin concentrations in some patients after 28 days. The most probable explanation for this observation is a confounding effect of prior medication despite a washout period in pretreated patients.

Concerning macroprolactin concentrations, no statistically significant alterations were observed during the study period in any of the treatment groups. However, at both baseline and 28 days, macroprolactin contributed to elevated prolactin levels in 2 patients taking risperidone and amisulpride, which is consistent with previous reports on the incidence of hyperprolactinemia due to excess macroprolactin content.[13,14] Consequently, macroprolactinemia should be taken into account when prolactin levels rise during SGA treatment, in particular as the symptoms of hyperprolactinemia are relatively common and nonspecific and are therefore likely to occur coincidentally in some patients with macroprolactinemia.[14–16]

In summary, this is the first investigation of the role of macroprolactin in SGA-induced hyperprolactinemia. Treatment with amisulpride and risperidone resulted in significantly increased prolactin levels. However, these were not attributable to excess macroprolactin content.

Table 1. Prolactin and Residual Prolactin Concentrations at Day 0 and After 28 Days of Second-Generation Antipsychotic Treatment[a]

Substance	Patients, Female/Male	Prolactin (Residual Prolactin)[b] Day 0	Day 28
Olanzapine	2/5	30.04 ± 28.28 (31.17 ± 28.26)	22.94 ± 13.54 (22.11 ± 12.75)
Clozapine	4/2	25.57 ± 16.10 (26.10 ± 15.61)	13.67 ± 15.62 (13.25 ± 6.51)
Ziprasidone	1/2	21.63 ± 9.92 (19.93 ± 9.92)	18.37 ± 9.08 (16.74 ± 10.01)
Risperidone	1/5	23.67 ± 13.53 (16.94 ± 5.27)	63.07 ± 26.19* (59.95 ± 30.58)
Amisulpride	2/5	17.06 ± 21.97 (18.28 ± 23.27)	63.99 ± 37.63* (69.90 ± 43.04)

[a]Values are expressed as mean ± SD μg/L.
[b]Asterisks indicate level of statistical significance between prolactin at day 0 and day 28 as determined by paired-samples rank test. No significant differences in prolactin vs. residual prolactin levels were found in any of the treatment groups.
*$p \leq .05$.

Data from this study were presented at the 13th annual meeting of the Austrian Society for Endocrinology and Metabolism; May 15–17, 2008; St. Wolfgang, Austria.

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Suicide Sex Ratio: The Interaction Between Mental Illness and Suicide Methods

Sir: A common explanation for the higher suicide rate in males is that men prefer violent and highly lethal methods.[1] Similarly, people with mental illness also tend to choose more violent and immediately lethal methods.[2,3] However, few studies have explored how suicide sex ratios vary according to the interactions between methods of choice and mental illness. This study examined how such an interplay determines the male-to-female suicide sex ratio in Taiwan.

Method. The records of all suicide deaths classified as ICD-9 (*International Classification of Diseases,* Ninth Revision) E950–959 from 2000 to 2004 were linked to the National Health Insurance (NHI) data files. The NHI program in Taiwan offered universal health care coverage, including inpatient, outpatient, and emergency room visits. Since participation in this program was mandatory, more than 99% of the entire population had coverage, and over 98% of the medical institutions in Taiwan were affiliated with the program.[4]

The top 4 methods of suicide—hanging (E953), charcoal burning (E952), solid and liquid poisoning (E950), and jumping from a high place (E957)—were analyzed. Since most of the E952 ("poisoning by other gases and vapors") suicides were by

Table 1. Male-to-Female Suicide Sex Ratios and Respective 95% Confidence Intervals (CIs) by Psychiatric Diagnosis and Suicide Method

	Total		Hanging		Charcoal Burning		Solid and Liquid Poisoning		Jumping From a High Place	
Group	Sex Ratio	95% CI	Sex Ratio	95% CI	Sex Ratio	95% CI	Sex Ratio	95% CI	Sex Ratio	95% CI
All	2.16		2.53		2.78		1.79		1.28	
Individuals without records of psychiatric treatment/diagnosis	3.74	3.51 to 4.00	4.25	3.82 to 4.77	4.23	3.70 to 4.89	3.08	2.70 to 3.54	2.01	1.63 to 2.52
Individuals with records of psychiatric treatment/diagnosis	1.51	1.44 to 1.58	1.84	1.71 to 2.00	1.71	1.50 to 1.97	1.28	1.16 to 1.42	1.09	0.96 to 1.24
Schizophrenia	1.60	1.42 to 1.81	1.81	1.45 to 2.30	2.43	1.64 to 3.91	1.86	1.43 to 2.48	1.18	0.93 to 1.51
Bipolar disorder	1.20	1.05 to 1.28	1.35	1.14 to 1.61	1.37	1.04 to 1.84	1.10	0.89 to 1.35	0.87	0.68 to 1.10
Depression	1.09	1.02 to 1.17	1.38	1.23 to 1.56	1.14	0.93 to 1.39	0.85	0.72 to 0.99	0.88	0.74 to 1.06

charcoal burning,[5] all deaths coded under E952 were categorized as charcoal burning suicide in this study. The psychiatric diagnoses evaluated were "schizophrenic spectrum disorder" (ICD-9-CM code 295.X), "bipolar disorder" (ICD-9-CM code 296.X excluding 296.2 and 296.3), and "depressive disorder" (ICD-9-CM codes 296.2, 296.3, 300.4). Method- and diagnosis-specific male-to-female suicide sex ratios and their corresponding 95% confidence intervals were calculated.

Results. Male-to-female suicide rate ratios varied by psychiatric diagnoses and suicide methods. Regardless of method, sex ratios decreased markedly in suicide victims with records of psychiatric treatment. The most marked decrease was in individuals treated for depressive disorder, followed by those treated for bipolar and schizophrenic disorders. Jumping from a high place was the method with the narrowest sex ratio, particularly among those with records of psychiatric disorders. In this subgroup, the suicide rates in women who were treated for bipolar and depressive disorders surpassed those of the men (Table 1). A reversed suicide sex ratio was also noted in cases of poisoning suicide who were previously treated for depressive disorder.

This study shows an "equalization" of suicide in men and women among those previously treated for psychiatric disorders. In subgroups utilizing certain suicide methods, such as depressive disorder in poisoning suicide and bipolar and depressive disorders in jumping suicide, the sex ratios are reversed. These findings challenge the dominant Western view that men have higher suicide rates because they tend to use methods that are more violent. The results here suggest that the role of gender in suicidal behavior is culturally embedded.[6] Hence, findings based on Western countries are not necessarily applicable to other cultures.

The results also suggest that in a clinical setting, the risk of suicide in women cannot be underrated. More effort should be put toward engaging men further to undergo treatment, as the higher suicide risk in men is observed mostly in individuals who had not sought help from the health care system.

This study specifically explores the interplay between psychiatric diagnosis and method of suicide in determining suicide sex ratios, an area that has rarely been examined before. However, there are several recognized limitations in the interpretation of the results. First, it is difficult to determine the reliability and validity of the claim data as well as the data from mortality files. Second, there may also be gender differences in psychiatric help-seeking behavior, and, as such, the decreased male-to-female suicide sex ratio in individuals treated for psychiatric disorders may be partly due to the lower rate of psychiatric consultations among men. Third, not all deaths classified under E952 are charcoal burning, and some may have been due to other sources of carbon monoxide poisoning. Last, the study was conducted in a single country, thereby limiting the applicability of the results to other cultural contexts.

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Late-Onset Manic Episode in a 91-Year-Old Man Without Previous Psychiatric History as a Unique Clinical Manifestation of a Pancreatic Neoplasm

Sir: In as many as half of the patients who are finally diagnosed with a carcinoma of the pancreas, symptoms of anxiety precede the knowledge of the diagnosis.[1] The link between pancreatic carcinoma and depression is also well known.[2] To our knowledge, no case of manic-like symptoms as a unique clinical manifestation of a pancreatic carcinoma has ever been presented.

We report here the case of a 91-year-old patient without a previous psychiatric history who developed a psychotic manic episode. Patients with a late-life onset of mania usually have an underlying medical or neurological disorder.[3,4] They also usually have no personal or family history of affective disorder, and they have a higher mortality rate than people with late-life depression.[4]

Case report. In May 2004, Mr. A, a 91-year-old white man, developed psychotic symptoms associated with a manic episode, experiencing a significant behavioral change that started 10 days prior to his admission without a clear triggering factor. He had no relevant previous psychiatric history nor substance misuse of any kind.

Upon initial presentation in the emergency room, Mr. A was hyper-alert and well oriented in space but just partially oriented to time, as he was oriented with respect to the month and the year, but not to the day. Euphoric, irritable, highly anxious, and dysphoric at times, he showed accelerated, circumstantial speech and, occasionally, flight of ideas. He developed megalomanic and paranoid delusions with high emotional implication and severely disruptive behavior. No alterations in perception were detected. In addition, Mr. A was hyperactive and had decreased need for sleep and appetite. He denied suicidal ideation and showed no insight about his clinical condition.

He was receiving treatment with doxazosin for hypertension; to our knowledge, there is no literature on manic symptoms induced by doxazosin, and no temporal correlation between initiation of drug treatment and onset of psychiatric symptoms could be found. It is interesting to note that in December 2003 the patient suffered from an intestinal pseudo-obstruction that remitted, presenting 2 months of residual diarrhea, normocytic-normochromic anemia of unknown origin, and a nonquantified weight loss since January 2004.

After an episode of psychomotor agitation, Mr. A was admitted to the psychiatric inpatient unit of a general hospital for diagnosis and treatment. Treatment with valproate, up to 900 mg/day, and quetiapine, up to 500 mg/day, was started. During the second week, a chronic inflammatory syndrome was diagnosed: it involved chronic anemia, increased erythrocyte sedimentation rate (ESR), and decreased pelvic muscle strength. Consequently, treatment with prednisone, up to 70 mg/day, was started, but at Mr. A's third week of admission, he suffered a switch to depression (depressed mood, psychomotor retardation, social withdrawal, global insomnia, and decreased appetite). Prednisone, quetiapine, and valproate were withdrawn upon the decision to administer 10 sessions of bitemporal electroconvulsive therapy (ECT), to which the patient showed partial response, and after the ECT sessions, drug therapy was started with sertraline, up to 100 mg/day, and trazodone, up to 50 mg/day.

One of the main goals during this 8-week hospitalization was to rule out any possible underlying medical (i.e., neurological) disorder. Normocytic-normochromic anemia was detected in a complete blood count. The rest of the laboratory tests, including biochemical, electrolytes, liver function tests, and thyroid screening, showed no alterations. Serology for hepatitis B, hepatitis C, human immunodeficiency virus, syphilis, and *Brucella* was negative as well. The patient's cerebrospinal fluid showed no significant alteration. No alterations were found in the chest x-ray or in the electrocardiogram (ECG). A head computed tomography scan at admission (repeated during hospitalization) showed mild leukoaraiosis. Results of an electroencephalogram (EEG) were nonspecific. Due to the finding of an increased ESR and an oligoclonal band upon protein electrophoresis, lumbar puncture was performed and reflected no alterations. Results of screenings for autoimmunity markers and tumor markers, as well as porphyrins and iron level, were also nonrelevant.

A first neuropsychological assessment done using the Cognitive Mini-Exam of Lobo et al.[5] at the third week after admission showed global maintenance of cognitive skills: the patient received a score of 35/35, suggesting no need for further investigation with neuropsychological examinations. We found that Mr. A displayed accelerated thought with normal processing ability and had no impairment in abstract thinking.

Given the results in the cognitive assessment, we ruled out delirium; moreover, the patient did not show fluctuation of his level of consciousness, had no sensory perception alterations, and had a subacute rather than acute onset of symptoms.

The patient achieved a full remission of his psychotic symptoms at the fifth week of admission. In addition, during the 8-week admission, Mr. A achieved remission of his affective episode, with improvements in his Young Mania Rating Scale[6] scores (score of 34 at admission, 0 at discharge). The patient was discharged in July 2004 with the following drug therapy: sertraline 100 mg/day plus trazodone 50 mg/day. No mood stabilizer was prescribed, but careful monitoring was advised.

In December 2004, 5 months after discharge, the patient was readmitted due to jaundice, acholia, and choluria, and weight loss of 14 kg, presenting episodic diffuse pain in the right hypochondrium. After laboratory tests, abdominal echography, cholangiopancreatography, and a biopsy, the diagnosis of a pancreatic neoplasm was finally reached, and the decision was made to provide palliative treatment.

The clinical presentation described in this case report encourages clinicians to rule out secondary mania. Even though no medical or neurological diagnoses were made during the manic episode, the pancreatic neoplasm could be associated with the affective symptoms through hormonal or immunological influence caused by direct or indirect action of the malignant tissue.

With respect to possible recommendations for assessing a manic episode in elderly patients, we believe that collateral information from caregivers and a family doctor is crucial; anxiety may be an early marker of a pancreatic carcinoma; a medication history, including over-the-counter and dietary supplements, should be obtained; and physical and neurological examination, a complete laboratory screening, ECG, EEG, and imaging studies of the brain should be performed. The goal is to make all reasonable efforts to rule out secondary mania. With respect to treatment recommendations, we observed the efficacy of standard medication, used at lower doses and with slower titration due to the age of the patient; ECT must also be considered. Specialists should be particularly aware of pharmacokinetic issues in the elderly and that close collaboration between the patient's psychiatrist and other

Table 1. Mother and Infant Concentrations of Bupropion in Breast Milk, Serum, and Urine at Trough and Peak Times[a]

		Trough			Peak									
ID	Dose (mg)	Maternal Serum (ng/mL)	Maternal Urine (ng/mL)	Breast Milk (ng/mL)	Maternal Serum (ng/mL)	Maternal Urine (ng/mL)	Breast Milk (ng/mL)	Milk/ Serum Ratio	Infant Urine (ng/mL)	Infant Dose (mg)	% of Maternal Dose	Infant Weight (kg)	Gestational Age (wk)	Infant Age (d)
A[b]	**150**	**ND**	**130.0**	**ND**	**170.0**	**> 1000.0**	**120.0**	**0.72**	**41.0**	**31.6**	**8.4**	**3.24**	**34**	**34**
B	150	150.0	ND	ND	64.0	440.0	ND	0.09	ND	5.1	1.4	3.41	39	14
B[c]	150	ND	ND	ND	140.0	> 1000.0	120.0	0.87		39.9	10.6	4.09	39	39
C	300[d]	13.5	26.0	8.5	24.5	410.0	24.5	0.87	ND	8.3	2.2	3.36	36	56
C[c]	300[d]	ND	18.5	ND	8.0	100.0	50.0	4.23	ND	15.5	4.1	3.76	36	70
D	300[d]	14.0	32.5	11.5	55.0	2800.0	60.0	1.04		28.6	7.6	5.33	41	90
Mean		33.8	37.8	9.2	76.9	958.3	64.1	1.30		21.5	5.7	3.86	37.5	50.5
SD		57.0	46.0	2.3	64.5	969.7	46.8	1.47		13.9	3.7	0.78	2.6	27.2

[a]The detection level for all samples was < 10 ng/mL. The limit of detection (< 10 or > 1000) was used in estimates.
[b]The infant with a detectable urine level of bupropion is indicated by boldface type and was 5½ weeks premature.
[c]Second clinic visit.
[d]Bupropion concentrations and estimated infant doses were dose-normalized to 150 mg.
Abbreviation: ND = not detectable.

specialists and careful monitoring of the patient after discharge are also needed.

Dr. Vieta has been a consultant for AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Pfizer, Novartis, sanofi-aventis, and Servier; and is a member of the speakers/advisory boards for and has received grant/research support from AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, Pfizer, sanofi-aventis, and Servier. The other authors report no financial or other relationships relevant to the subject of this letter.

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Bupropion Levels in Breast Milk for 4 Mother-Infant Pairs: More Answers to Lingering Questions

Sir: Bupropion is an atypical antidepressant labeled for depression and smoking cessation. There is limited pharmacokinetic information about bupropion in the perinatal period.[1–3] The purposes of this study were (1) to provide additional estimates of the concentration of bupropion in breast milk relative to maternal serum levels in nursing women and (2) to estimate the residual concentration of bupropion in nursing infants.

Method. Postpartum nursing mothers actively taking bupropion for smoking cessation or depression were recruited between November 2000 and December 2002. Participants came to the clinic after steady-state concentrations had been reached (at least 10 days at a constant dose). Maternal trough serum, breast milk, and urine samples were collected before the participants took their daily dose of bupropion SR (150 or 300 mg). After 2 hours, study personnel collected maternal peak serum, breast milk, and urine samples and the first infant urination. All bupropion concentrations were measured using gas chromatography. Metabolite concentrations were not measured. When there were no detectable levels of bupropion, the lower limit of quantification (10 ng/mL) was used. Bupropion values were dose-normalized to 150 mg.

Samples were collected from 6 postpartum breastfeeding women between 22 and 40 years of age. Two women were excluded from the analyses due to noncompliance as evidenced by no detectable peak or trough bupropion concentrations in serum, breast milk, or urine. The infants ranged in age from 13 to 90 days at the first data collection. Two women returned for repeat samples.

Results. Bupropion concentrations were variable at both peak and trough. Mean breast milk concentrations were 64.1 ng/mL at peak and 9.2 ng/mL at trough (Table 1). Bupropion was detected in only 1 of the 4 infant urine samples (41 ng/mL); the infant was nearly 6 weeks premature. The average milk-serum ratio was 1.30 (range, 0.09–4.23).

The Atkinson model[4] was used to estimate the infant daily dose of bupropion:

$$\text{infant dose} = [(\text{peak}_{BM} + \text{trough}_{BM})/2 \times 0.15 \text{ L/kg} \times \text{infant weight kg}]/(150/\text{maternal kg})$$

where BM = breast milk, 60 kg was used as the average maternal weight, and 0.15 L/kg was used as the average milk intake per

kg. The estimated bupropion dose that each infant received was 21.5 mg, which was 5.7% of the weight-adjusted maternal dose.

There was substantial individual variation in peak serum, urine, and breast milk bupropion concentrations in this study sample. The peak serum bupropion concentrations were somewhat higher than those found in previous studies for bupropion SR.[2,3] These observed serum levels are more consistent with the range of serum levels found in treatment responders. Peak breast milk concentrations were similar to those reported by Haas et al.[3]; trough breast milk concentrations were low or nondetectable. Metabolites were not measured and were most likely present in higher concentrations than the parent compound. While previous reports found no evidence of bupropion in infant plasma,[1,2] this study found bupropion concentrations in the urine of 1 infant. The average infant dose was 5.7% of the weight-adjusted maternal dose, which indicates limited exposure to bupropion in breastfed infants.

On the basis of these observational data, the risk of systemic exposure to bupropion in breastfed infants would appear minimal. The need for data from other nursing pairs remains high.

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