Prevalence of Hyperprolactinemia in Schizophrenia: Association With Typical and Atypical Antipsychotic Treatment

Julie Montgomery, M.S.W.; Elizabeth Winterbottom, M.S.W.; Meera Jessani, M.D.; Eva Kohegyi, M.D.; Janice Fulmer, R.N.; Bette Seamonds, Ph.D.; and Richard C. Josiassen, Ph.D.

Objective: To evaluate the prevalence and severity of hyperprolactinemia among a large sample of patients with schizophrenia and related psychotic disorders treated with typical and atypical antipsychotic medications.

Method: Three electronic databases (general medical, psychiatric, and pharmacologic) containing the census data from November 2002 through March 2003 for a state-funded, inpatient hospital serving the chronically mentally ill were merged (N = 470). This database was purged of patient names, while the unique hospital identification number and demographic variables in each record were retained. These records were then screened to exclude patients with medications (except neuroleptics) or medical conditions known to elevate or suppress prolactin, leaving an overall sample (N = 422) in which to evaluate the prevalence of hyperprolactinemia. The sample was composed of patients with DSM-IV schizophrenia (N = 213), other related psychotic disorders (N = 131), mood disorders (N = 44), and other disorders (N = 34).

Results: For the overall sample (N = 422), which combined men and women, the mean serum prolactin level was 41.5 ng/mL; 290 of 422 patients were above the normal range. For women (N = 133), the mean serum prolactin level was 57.9 ng/mL, and 67% had levels above normal. For men (N = 289), the mean level was 33.9 ng/mL, with a 70% prevalence of hyperprolactinemia. While age did not influence the prevalence of elevated prolactin among men, age (reflecting reproductive status) was a significant variable in women; older age was associated with lower prolactin levels. For the study sample, a highly significant correlation was observed between neuroleptic dose (chlorpromazine equivalent) and serum prolactin level; however, this relationship was not determined on a medication-by-medication basis. Medications known to elevate prolactin were associated with higher prevalence rates of hyperprolactinemia, and "prolactin-sparing" medications had lower prevalence rates. However, when they were used in combination, the prolactin-elevating medication overwhelmed the effects of prolactin-sparing medication.

Conclusions: This study suggested that neuroleptic treatment of schizophrenia is strongly associated with hyperprolactinemia and showed important differences between prolactin-sparing and prolactin-elevating medications.

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Received Oct. 6, 2003; accepted April 8, 2004. *From the Arthur P. Noyes Research Foundation, Norristown, Pa. (Mss. Montgomery and Winterbottom and Drs. Jessani, Kohegyi, and Josiassen); the Department of Social Work, West Chester University, West Chester, Pa. (Mss. Montgomery and Winterbottom); the Department of Psychiatry, University of Pennsylvania, Philadelphia (Drs. Kohegyi and Josiassen); Norristown State Hospital, Norristown, Pa. (Ms. Fulmer); and Mercy Suburban Hospital, Norristown, Pa. (Dr. Seamonds).*

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Corresponding author and reprints: Richard C. Josiassen, Ph.D., Arthur P. Noyes Research Foundation, 1001 Sterigere St., Norristown, PA 19401 (e-mail: richardjosiassen@noyesfoundation.net).

Elevation of serum prolactin (hyperprolactinemia) is a clinical disorder often seen among people with schizophrenia. High levels of serum prolactin may stem from a variety of etiologies, including pregnancy, lactation, and prolactinomas, but in those with schizophrenia, hyperprolactinemia most commonly results from treatment with antipsychotic agents. Kleinberg et al.[1] first reported that treatment with antipsychotic medication is associated with increased prolactin secretion, and it was quickly accepted that all of the clinically effective first-generation antipsychotics elevate prolactin by inhibiting the action of dopamine on D_2 receptors on the anterior pituitary gland.[2–4] Until the early investigations of clozapine,[5] hyperprolactinemia was assumed to be the inevitable consequence of effective antipsychotic treatment, and little attention was given to its possible health consequences.[6–8]

The function of prolactin in healthy humans is complex. Schizophrenia and its treatment only compound this complexity. The best-characterized functions subserved by prolactin include lactation, regulation of gonadal ste-

roids, and reproductive function. The full extent of sexual and reproductive morbidity associated with neuroleptic-induced hyperprolactinemia has not been adequately assessed. Most patients with schizophrenia are sexually active, and many have long-term partners.[9] While unmedicated patients tend to experience a reduced libido, probably the result of their primary illness and its social consequences, other sexual and reproductive dysfunctions are not typical in these patients.[10] When serum prolactin levels are high, however, sexual and reproductive side effects appear to be invariably present,[11–15] although contradictory findings from a large population study have been reported.[16]

Hyperprolactinemia and reduced levels of sex steroids resulting from hyperprolactinemia may have other health consequences. Reviews[7,8] have summarized the modest literature, which suggests that, along with sexual and reproductive consequences, sustained prolactin elevation may adversely affect levels of anxiety and hostility, immune function, osmoregulation, and cardiovascular function. Loss of bone mineral density leading to osteoporosis has also been reported.[17–19] However, the short- and long-term implications of hyperprolactinemia have received limited attention.

In this retrospective study, we examined the prevalence and severity of hyperprolactinemia in a large sample of chronically psychotic inpatients residing in a state hospital. The specific aims were as follows. (1) To collect evidence regarding the prevalence and severity of hyperprolactinemia in this population. Though hyperprolactinemia is widely recognized among psychotic patients, its prevalence in a naturalistic setting has seldom been studied. Recent publications[20,21] report prevalence findings among highly screened patients selected for clinical trials of typical neuroleptics and risperidone. We report a hospital-based sample of patients treated with typical and atypical antipsychotics. (2) To explore the extent to which hyperprolactinemia is directly related to specific typical and atypical antipsychotics and dosages. (3) To characterize the dose/prolactin response relationships. (4) To explore some health consequences of elevated serum prolactin levels.

METHOD

Subjects and Procedural Details

This study was conducted at Norristown State Hospital (Norristown, Pa.), a state-funded, inpatient hospital serving the chronically mentally ill in Philadelphia and surrounding counties. The hospital census (N = 470) at the time of this study constituted the initial sample. Norristown State Hospital policy encourages all patients to receive an annual medical examination, including a comprehensive clinical panel, electrolytes, and prolactin assay. Medical referrals are also common. This information is maintained electronically. Therefore, this project was considered a zero-risk quality-assurance project and was authorized by the local institutional review board and the Norristown State Hospital administration.

Three electronic databases were merged to create a master database on which statistical analyses were performed. The electronically stored hospital census for November 2002 through March 2003 was obtained and purged of all patient names. Each record's unique hospital identification number and other demographic variables, such as age, gender, race, and diagnosis, were retained. Using the identification numbers, we retrieved the most recent clinical laboratory values. This allowed patient-specific prolactin levels to be merged into the master database, along with the comprehensive clinical panel and electrolytes and the collection dates of samples. Next, based on the date of each prolactin sample, electronically stored medication records were obtained for each patient. Specific medications and doses were obtained for each patient; these records made it possible to ensure that the medications had been stable in terms of class and dose for at least 1 month prior to the prolactin level assay. For a limited number of patients, the medication information was not temporally related to the date of the prolactin sample, and in such cases a preceding prolactin sample was selected and matched. In some cases, data on prolactin levels and stable medications could not be obtained, and in other cases, no recent clinical laboratory values were available due to patient refusal or other administrative problems. The records of this initial hospital population (N = 470) were further screened to exclude any patient with medications (except neuroleptics) or medical conditions known to elevate or suppress prolactin.

Of the initial hospital census, then, 48 patients were excluded from further analysis, resulting in an overall study sample (N = 422) for whom prolactin levels were available. The mean (SD) age of the overall sample was 47.4 (13.9) years; the male patients (N = 289) ranged in age from 20 to 85 years, and the female patients (N = 133) ranged in age from 20 to 95 years.

Next, this study sample (N = 422) was evaluated regarding neuroleptic status. Forty additional patients were excluded because they were unmedicated due to health reasons or refusal of treatment or were receiving treatment other than antipsychotics (e.g., antimanic drugs). This exclusion resulted in a refined sample of patients who were treated only with antipsychotic medications (N = 382) and for whom both prolactin levels and reliable medication information (class, dose, and dates) were available. Data on demographics and prolactin levels for this refined sample and for the overall sample are shown in Table 1.

Definition of Hyperprolactinemia

All clinical laboratory samples had been collected in the morning under fasting conditions and sent to

the Mercy Suburban Laboratory (Norristown, Pa.), where electrochemiluminescence was performed for assays of prolactin. This technology has a prolactin-measuring range of 0.47 to 470 ng/mL. Within our prolactin dataset, the values ranged from 2.7 to 255.1 ng/mL and were within the sensitivity of this technology. Each subject's prolactin level was entered into the master database as both a *continuous* variable (actual prolactin level) and a *dichotomous* variable (normal or abnormal). The designation of normal or abnormal was based on laboratory norms defined separately by gender (men, 4.1–18.4 ng/mL; women, 3.0–26.0 ng/mL). Any value exceeding the gender-specific upper limits was considered hyperprolactinemia. Thus, even the slightest prolactin elevations of unknown clinical significance received this designation.

Chlorpromazine Equivalents

Each patient's treatment record was examined to determine the class and dose of each neuroleptic medication and to ensure that treatment had been stable for at least 1 month prior to the prolactin assay. Daily doses were converted to chlorpromazine (CPZ) equivalents (H. Y. Meltzer, M.D., oral communication, April 2004; Kane[22]). Of the sample treated with neuroleptics (N = 382), 190 were being treated with monotherapy and the remainder (N = 192) were being treated with 2 or more neuroleptics. Those treated with monotherapy were receiving the following medications: chlorpromazine (5/190), fluphenazine (11/190), haloperidol (9/190), perphenazine (2/190), thioridazine (1/190), clozapine (19/190), ziprasidone (2/190), risperidone (56/190), quetiapine (18/190), and olanzapine (67/190).

Extreme Prolactin Groups

From the refined patient group (N = 382), "high-prolactin" and "low-prolactin" individuals were identified. The high-prolactin group included 21 patients (14 men and 7 women) with a mean serum prolactin level of 136.7 ng/mL (range, 74.8–255.1 ng/mL). This high-prolactin group was then matched by gender, age (within 2 years), and diagnosis with patients showing normal prolactin levels, with a mean level of 12.1 ng/mL (range, 4.7–21.4 ng/mL). The comprehensive clinical panel and electrolytes records for these extreme groups were statistically compared.

Symptom Questionnaire

Next, institutional review board approval was sought to interview these individuals regarding sexual and reproductive functioning. Of the original sample of 42 subjects, only 19 participated in the direct interview; the others either had been discharged from the hospital already or refused to be interviewed. Sexual and reproductive symptoms were assessed by means of a semistructured questionnaire administered by one of the authors (J.F.), who coordinated family planning education throughout the hospital but remained blinded as to subjects' prolactin status. Women were asked open-ended questions that focused on 8 specific items related to menstrual symptoms (e.g., fewer days of flow) and breast changes (e.g., unusual breast tenderness). Men were asked the same questions regarding breast changes, as well as questions about penile function (e.g., difficulty achieving erection). The presence and severity of symptoms were rated using a range from 0 (not present) to 5 (severe), as well as by asking how much the symptoms bothered the individual on a numeric scale.

Table 1. Demographic, Diagnostic, and Prolactin Level Data for the Overall Sample (N = 422) and the Subgroup Receiving Antipsychotics (N = 382)

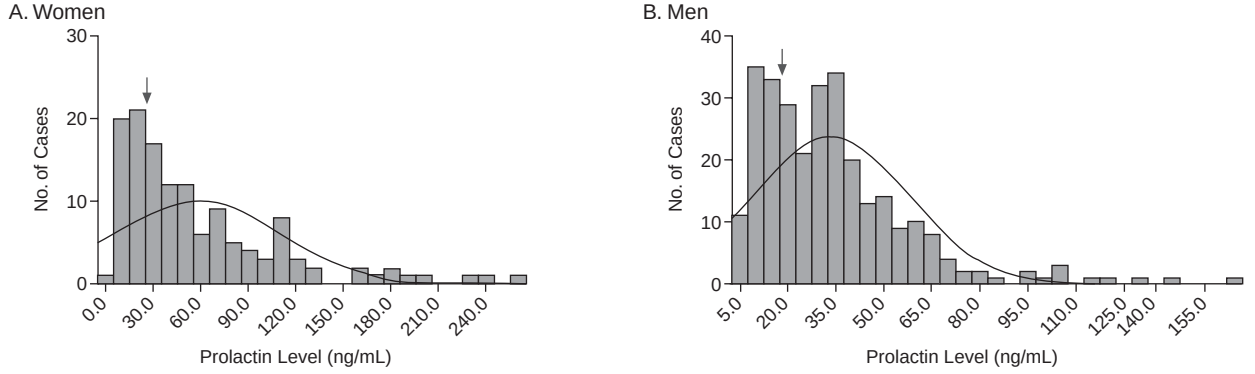
Variable	Overall Sample	Antipsychotic Subgroup
Age, y		
Mean (SD)	47.4 (13.9)	48.1 (13.7)
Range		
All	20–95	20–95
Men	20–85	20–85
Women	20–95	22–95
Gender, N (%)		
Male	289 (68)	264 (69)
Female	133 (32)	118 (31)
Prolactin level, ng/mL		
Mean (SD)	41.5 (37.1)	42.1 (36.7)
Range	2.7–255.1	2.7–255.1
Patients with prolactin elevation, %[a]		
All	68	71
Men	70	72
Women	67	68
Patients with prolactin elevation 2 × normal, %[b]		
All	36	37
Men	35	36
Women	41	42
Diagnosis, N		
Psychotic disorders	344	323
Schizophrenia	213	208
DSM-IV subtypes		
295.1-Disorganized	7	7
295.3-Paranoid	93	90
295.6-Residual	2	2
295.9-Undifferentiated	111	109
Schizoaffective disorder	108	96
Psychotic disorder NOS	19	16
Other psychotic disorders	4	3
Mood disorders	44	29
Major depressive disorder	6	5
Bipolar disorder	27	21
Other mood disorders	11	3
Other	34	30

[a]Prolactin level elevated beyond gender-specific norms.
[b]Prolactin level elevated 2 times or more beyond gender-specific norms.
Abbreviation: NOS = not otherwise specified.

Presentation of Data

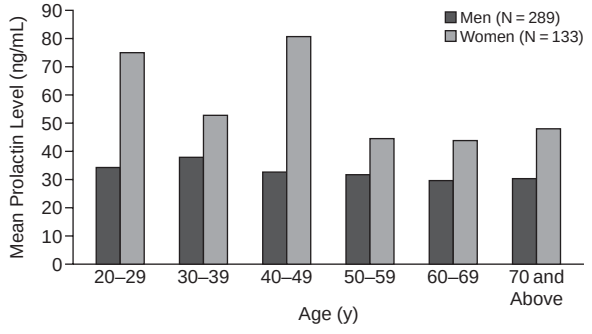
We report first the prevalence of hyperprolactinemia in the hospital-wide sample (N = 422) and the prevalence rates for the refined sample treated with antipsychotic

Figure 1. Distribution of Serum Prolactin Levels for (A) Women (N = 133) and (B) Men (N = 289)[a]



[a]Mean (SD) prolactin levels were 57.9 (52.0) ng/mL for women and 33.9 (24.2) ng/mL for men. The curves represent mean and SD values. The arrows represent the gender-specific cutoff values for the upper end of the normal range; it should be noted that the mean prolactin levels for both genders far exceed these cutoff values.

Figure 2. Serum Prolactin Levels by Gender Partitioned Into Age Groups



medication (N = 382), including an evaluation of individual medication effects. Second, we report the overall correlation between prolactin levels and CPZ equivalence values. Finally, we discuss health consequences in the "extreme" prolactin groups.

RESULTS

Hospital-Wide Prevalence of Hyperprolactinemia

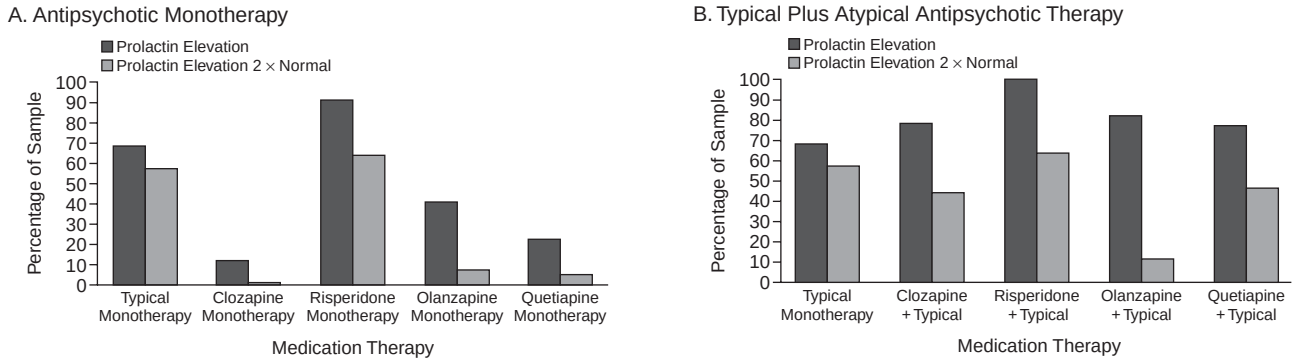
For the hospital-wide population (excluding those with medical conditions known to elevate or suppress prolactin) (N = 422), the group mean (SD) serum prolactin level was 41.5 (37.06) ng/mL (range, 2.7–255.1 ng/mL). Figures 1A and 1B display the serum prolactin levels separated by gender with laboratory norms indicated. For women (N = 133), the group mean serum prolactin level was 57.9 (51.99) ng/mL (range, 4.4–255.1 ng/mL). Based on gender-specific laboratory norms, the prevalence of hyperprolactinemia among female patients (prolactin level of > 26.0 ng/mL) was 67% (89/133). For men (N = 289), the group mean prolactin level was 33.9 (24.22) ng/mL (range, 2.7–166.1 ng/mL) with a 70% (201/289) prevalence of hyperprolactinemia (prolactin level > 18.4 ng/mL). The difference in prevalence rates between men and women was not statistically significant (χ^2 test). However, these rates did vary by age. As seen in Figure 2, prolactin levels remained uniform for men across the decades, while an obvious reduction in prolactin occurred in women as they aged. Results of a t test comparison between women 50 years of age and above (N = 71) and those below 50 years of age (N = 62) were statistically significant (t = –2.74, df = 111, p < .008).

Prevalence of Hyperprolactinemia With Neuroleptic Treatment

While prolactin levels were available for the group as a whole, 40 patients were not being treated with antipsychotic medications and were removed from the refined sample. As seen in Table 1, the removal of these patients from the refined group did not markedly alter the group demographics. The prevalence of hyperprolactinemia among the neuroleptic-treated patients (mean serum prolactin level = 42.1 ng/mL) was 270/382 (71%), with 143/382 (37%) exceeding twice the normal range of prolactin values.

For patients treated with monotherapy, prolactin levels varied considerably according to medication. Figure 3A illustrates the prevalence rates of hyperprolactinemia and the well-documented "prolactin-sparing" or "prolactin-elevating" properties of each medication. For patients treated with conventional antipsychotics, 19 (68%) of 28 had elevated prolactin levels, with 57% showing a greater than 2-fold increase above normal. With newer atypical antipsychotics, the prevalence of hyperprolactinemia was as follows: clozapine 2/19 (11%, with 0% having a 2-fold increase), risperidone 51/56

Figure 3. Prevalence of Hyperprolactinemia Among Patients Receiving Antipsychotic Monotherapy and Typical Plus Atypical Antipsychotic Therapy



(91%, with 64% having a 2-fold increase), olanzapine 27/67 (40%, with 7% having a 2-fold increase), and quetiapine 4/18 (22%, with 5% having a 2-fold increase). Again, hyperprolactinemia among male patients was not age-related, whereas reproductive status influenced the prevalence of hyperprolactinemia in female patients.

What happens when prolactin-sparing and prolactin-elevating medications are combined? For those patients treated with a combination of conventional antipsychotics and 1 atypical medication, the prevalence of hyperprolactinemia was consistently high. Figure 3B depicts these findings as follows: conventional plus clozapine 7/9 (78%, with 44% having a 2-fold increase), conventional plus risperidone 24/24 (100%, with 63% having a 2-fold increase), conventional plus olanzapine 36/44 (82%, with 11% having a 2-fold increase), and conventional plus quetiapine 27/35 (77%, with 46% having a 2-fold increase).

Dose-Response Relationship to Prolactin

For the group as a whole (N = 382), a significant linear relationship existed between oral dosage (CPZ equivalents) and serum prolactin levels ($r = .201$, $p < .0005$). However, analysis of the smaller groups treated with monotherapy (using the actual dose in milligrams, not a CPZ equivalent) revealed a lack of correlation between dose and serum prolactin; this was also the case when correlations were performed separately by gender, even when the effects of age were removed via partial correlation.

Comparison of Laboratory Values in the Extreme Groups

Next, the high- and low-prolactin groups were compared on comprehensive hematology and electrolyte laboratory values measured at the same time as the prolactin levels. Only 4 values yielded statistically significant group differences: red blood cell count (high-prolactin group < low-prolactin group), chloride (high-prolactin group > low-prolactin group), globulin (high-prolactin group > low-prolactin group), and albumin:globulin ratio (high-prolactin group < low-prolactin group).

Comparison of Sexual and Reproductive Symptoms

Direct patient interviews revealed that sexual and reproductive symptoms varied greatly. Therefore, rather than analyzing individual items, we tallied the number of endorsed symptoms (maximum possible of 8 for women and 9 for men). The mean (SD) numbers of endorsed items for the high- and low-prolactin groups were 2.7 (2.6) and 1.5 (1.5), respectively ($t = 1.99$, $df = 17$, $p < .063$). When analyzed by gender, the mean (SD) numbers of endorsed items for the high- and low-prolactin female groups were 3.6 (3) and 1.3 (2.2), respectively (t value = 2.59, $df = 6$, $p < .04$), while the numbers for the high- and low-prolactin male groups were 2.0 (2.8) and 1.8 (0.3) ($p = NS$). For women, the most frequently reported symptoms were amenorrhea and galactorrhea. Among the men, both the high- and low-prolactin groups reported inhibition of ejaculation and erection disturbance, with 1 high-prolactin man reporting breast sensitivity.

DISCUSSION

A large population of medicated state hospital patients was evaluated for hyperprolactinemia. The level of prolactin in unmedicated patients is usually within normal limits.[23] All conventional antipsychotic agents elevate serum prolactin,[24] and initially a high correlation between prolactin level and therapeutic efficacy was suggested.[3] As a result, hyperprolactinemia became a common clinical disorder and was considered the inevitable consequence of antipsychotic treatment. In our sample, which included those treated with both conventional and atypical antipsychotics, the prevalence of hyperprolactinemia was nearly 70% for the hospital census. For women

Table 2. Effect of Antipsychotic Medications on Prolactin Level

Prolactin Elevating	Prolactin Sparing
Traditional neuroleptics	Clozapine
Risperidone	Olanzapine
	Quetiapine
	Ziprasidone
	Aripiprazole

(N = 133), the prevalence was 67%, with a mean prolactin level of 57.9 ng/mL (nearly 3-fold the upper limit of normal). For men (N = 289), the prevalence was 70%, with a mean prolactin level of 33.9 ng/mL (nearly 2-fold the upper limit of normal). Even when medical exclusion criteria were applied, prevalence estimates were virtually unchanged.

Although the differential prolactin-elevating and prolactin-sparing properties of each medication are well documented, information about the actual prevalence of hyperprolactinemia among schizophrenic populations has been lacking. Available data from healthy populations suggest a very low prevalence rate of 0.4% and a rate of 9% to 17% in women with reproductive disorders.[25] Among our sample of patients treated with both conventional and atypical antipsychotics, a much higher prevalence was found, raising several questions, which follow.

First, are the prolactin-elevating and prolactin-sparing properties of individual medications observed in naturalistic populations? Table 2 summarizes the effects on prolactin of currently available drugs. Ziprasidone and aripiprazole were not being used at the hospital at the time of this survey. Among patients treated with monotherapy, though, the relative prolactin levels were as expected for conventional antipsychotics (68% prevalence, with 57% greater than 2-fold prolactin increase above normal), clozapine (11%, with 0% having a 2-fold increase), risperidone (91%, with 64% having a 2-fold increase), olanzapine (40%, with 7% having a 2-fold increase), and quetiapine (22%, with 5% having a 2-fold increase). Given the relative prolactin-elevating and prolactin-sparing properties of available antipsychotic medications, resolving hyperprolactinemia and possible complications is now a treatment option.

It could be argued, however, that the primary purpose of treatment with antipsychotics is to reduce psychotic symptoms and that treating psychotic patients with complex medical complications is an unusual challenge. Little experience has been reported in this area, but as more patients are treated within the context of comprehensive care, experience and knowledge will grow. Such a complex situation cannot be addressed without controlled studies involving interrelated disciplines.

Second, what is the result on serum prolactin level of combining prolactin-elevating and prolactin-sparing medications? Within the confines of our sample, combining conventional neuroleptics with newer atypical medications elevated serum prolactin in every case: conventional plus clozapine (78%, with 44% having a 2-fold increase), conventional plus risperidone (100%, with 63% having a 2-fold increase), conventional plus olanzapine (82%, with 11% having a 2-fold increase), and conventional plus quetiapine (77%, with 46% having a 2-fold increase). Clearly, the prolactin-sparing properties of the newer atypicals are overwhelmed by the prolactin-elevating properties of conventional medications.

Third, are prolactin levels dose-related for individual medications? The lack of consensus regarding a method for converting neuroleptic doses into a common metric is problematic and raises questions about the validity of CPZ equivalents and prolactin level correlations. Interestingly, however, when the actual doses in milligrams of individual medications were used in the analysis, the dose/prolactin correlations failed to reach statistical significance. While the time to achieve maximal prolactin increase is well established for each drug based on studies of single-dose effects, continued-administration studies (more closely resembling clinical practice) are lacking. It seems that once a patient is taking antipsychotic medication daily, prolactin elevation persists, although with fluctuations. The prolactin response to neuroleptic treatment is also a measure of the "bioavailability" of the medication, which varies by individual. Even in our sample, some of the highest serum prolactin levels were obtained from patients treated with very low doses of conventional neuroleptics and vice versa. Thus, serum prolactin level appears to be directly influenced by dose with some unspecified level of fluctuation, but the degree of correlation between dose/serum prolactin level cannot be extrapolated from individual cases to the group.

Fourth, what, if any, are the short- and long-term medical consequences of hyperprolactinemia? The greatest concern is probably the possibility of developing hypogonadism (estrogen deficiency in women and testosterone deficiency in men), because this condition can produce significant morbidity.[7,8,26] Clinical experience reveals that antipsychotic-induced prolactin elevation is a significant factor in inducing sexual dysfunctions, amenorrhea, galactorrhea, and gynecomastia, but the phenomenon has been understudied. Because people with schizophrenia receive long-term treatment, it is important to study the long-term effects of elevated prolactin, as well as the interactions among development, aging, and the chronic use of antipsychotics. The absence of clinical laboratory findings in our extreme groups is somewhat encouraging. However, these standard laboratory measures are not the best ways to assess chronic prolactin elevation as a possible risk factor for immune disorders, osteoporosis, and heart disease, nor would they reflect effects on the maturing reproductive systems of adolescents. In general, the safety record with antipsychotic treatment is good, and at

present the challenge for the clinician is to monitor serum prolactin level closely in complex cases. The newer prolactin-sparing medications provide important alternatives that can be utilized as needed within the context of comprehensive care.

Limitations of the Study

The sample had a wide age range (20–95 years), which implies a heterogeneity of treatment history of unknown central nervous system consequences. Included in this sample were patients known to have received somatic treatments that predated medication (frontal lobe surgery, electroconvulsive therapy, and insulin coma therapy), patients who had taken typical neuroleptic medications long term in various combinations and used very high doses at times, and still others who were treated only with atypical antipsychotic medications. The variety of neuroadaptive changes in brain neurotransmitter systems that may have occurred following these treatments remains unspecified, and their effects are unknown. Some early findings suggest that, over time, tolerance may develop in the prolactin-elevating effect of neuroleptic drugs.[26] Another limitation is that, unfortunately, our data were collected at a time when very few patients were receiving ziprasidone or aripiprazole.

Routine measures of estrogen and testosterone or metabolites reflecting rate of bone turnover would have greatly enhanced the dataset, but these measures were available only for individuals already known to have a related medical condition. Including these measures from a medically referred subgroup would have introduced a selection bias that would have obscured the meaning of any findings. Yet, even with these limitations in mind, these prevalence findings from a naturalistic setting should be considered unique and valuable data. It is increasingly difficult to gather prevalence data, since it is rarer now for psychiatric patients to spend much time within a psychiatric hospital.

CONCLUSIONS

The prevalence of hyperprolactinemia is very high among people with schizophrenia who are being treated with antipsychotic medication. The level at which hyperprolactinemia becomes a meaningful health risk, however, is uncertain. Much of the knowledge regarding the influences of prolactin has been learned from medical patients with prolactinomas.[27] In otherwise medically healthy women, prolactinomas are detected when they are small and the prolactin level is only moderately elevated, from 30 to 300 ng/mL, which is the approximate range seen among the female patients in our study (4.4–255.1 ng/mL). In contrast, prolactinomas in men are usually not detected until they are large, and these men often have prolactin levels over 500 ng/mL, well above the range obtained from men in our sample (2.7–166.1 ng/mL). The clinical presentation of prolactinomas in the "normal" population is generally similar to that seen with neuroleptic-induced hyperprolactinemia, although the size of prolactinomas in males can lead to compression of the optic nerve and headache, which are not seen with neuroleptically induced prolactin elevation. Whether the literature documenting the consequences of prolactinomas in medical patients can be extrapolated to neuroleptic-treated patients is an open question. However, hyperprolactinemia has both direct actions on the brain and indirect effects via suppression of sex hormones. Of greatest concern with hyperprolactinemia is the possibility of developing hypogonadism, as described earlier in this section.[8] Serum prolactin elevation is probably an important factor in inducing short-term sexual dysfunction as well as a causal factor in amenorrhea and galactorrhea. These short-term consequences of elevated prolactin can be understood and treated.

The potential long-term effects of hyperprolactinemia are much more controversial. For example, since the reproductive system matures during adolescence, should prolactin levels in this group be monitored more closely to minimize neuroendocrine effects? Unfortunately, an unambiguous understanding of the long-term consequences of elevated prolactin is complicated by the interaction of chronic neuroleptic use and aging, which in and of itself can increase the risk of immune function disorders, osteoporosis, and heart disease. Until these long-term questions are answered, the challenge for clinicians will be to closely monitor patients with schizophrenia who are treated with antipsychotic medications for elevated prolactin and its potential consequences.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, Fazaclo, and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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