CME ACTIVITY

Sponsored by Physicians Postgraduate Press, Inc.

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education. To obtain credit, please read the following article and complete the posttest as instructed on page 68.

CME Objectives

After completing this CME activity, the psychiatrist should be able to:

- Consider how gender differences in older patients may affect the clinical presentation of schizophrenia
- Examine how age at onset and gender may interact in the clinical presentation of schizophrenia in geriatric patients

Statement of Need and Purpose

Physicians responding to articles in *The Journal of Clinical Psychiatry* and its related CME activities have indicated a need to know more about the diagnosis and management of psychosis in older patients. This CME enduring material presents current information to address that need. There are no prerequisites for participating in this CME activity.

Accreditation Statement

Physicians Postgraduate Press is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

Credit Designation

Physicians Postgraduate Press designates this educational activity for a maximum of 1 hour in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Faculty Disclosure

In the spirit of full disclosure and in compliance with all Accreditation Council for Continuing Medical Education Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows:

Drs. Lindamer, Lohr, Harris, McAdams, and Jeste have no significant commercial relationships to disclose relative to the presentation.

Discussion of Investigational Information

During the course of their talks and discussions in this *Journal*, faculty may be presenting investigational information about pharmaceutical agents that is outside Food and Drug Administration–approved labeling. This information is intended solely as continuing medical education and is not intended to promote off-label use of any of these medications. Please refer to page 67 for a list of indications of off-label usage describing any medication discussed in this enduring material that, in the authors' clinical estimation, is outside the manufacturer's current recommendations for standard prescribing practices.

Gender-Related Clinical Differences in Older Patients With Schizophrenia

Laurie A. Lindamer, Ph.D.; James B. Lohr, M.D.; M. Jackuelyn Harris, M.D.; Lou Ann McAdams, Ph.D.; and Dilip V. Jeste, M.D.

Background: Gender differences in the clinical presentation of young patients with schizophrenia have been well-documented, yet few studies have investigated gender-related clinical differences in older patients. Furthermore, the symptoms of late-onset schizophrenia have been described, but the interaction between gender and age at onset has not been examined.

Method: In an older (46–85 years of age) outpatient sample, we assessed clinical characteristics of women and men with early-onset schizophrenia (N = 90) and late-onset schizophrenia (N = 34). Subjects did not differ with respect to age, education, ethnicity, severity of depression, daily neuroleptic dosage, subtype of schizophrenia, total score on the Mini-Mental State Examination, or severity of overall psychopathology. Diagnosis was made using the Structured Clinical Interview for the DSM-III-R or DSM-IV.

Results: A significantly greater proportion of women had late-onset schizophrenia (41% vs. 20%), and women overall had more severe positive psychotic symptoms. Although there was no overall gender difference in severity of negative psychotic symptoms, women with late onset had significantly less severe negative symptoms than men with early onset, men with late onset, and women with early onset. Furthermore, age at onset of schizophrenia was inversely correlated with severity of negative symptoms for women, but not for men. These results indicate that women overall may develop more severe positive symptoms than men, and that when women develop schizophrenia after age 45, they may suffer less severe negative symptoms than men or than women with earlier onset. Our results suggest that some of the clinical differences between lateonset and early-onset schizophrenia may relate to gender effects, and that there may be inherent differences in the clinical presentation of schizophrenia that are related to gender and gender by age at onset interactions.

Conclusion: These differences may reflect the influence of sex hormones and menopause on the clinical presentation of schizophrenia or the possible existence of an "estrogen-related" form of schizophrenia in women with late-onset schizophrenia.

(J Clin Psychiatry 1999;60:61–67)

Received Aug. 14, 1996; accepted April 14, 1998. From the Department of Psychiatry, University of California, San Diego (all authors), and Psychiatry Services, San Diego VA Medical Center (Drs. Lindamer, Lohr, Harris, and Jeste).

Supported in part by grants MH-43693, MH-51459, MH-45131, MH-49671, and MH-01580 from the National Institute of Mental Health, Rockville, Md.; the National Alliance for Research on Schizophrenia and Depression; and the Department of Veterans Affairs.

Reprint requests to: Laurie A. Lindamer, Ph.D., San Diego Veterans Affairs Medical Center, 116A, 3350 La Jolla Village Dr., San Diego, CA 92161.

ender differences in the clinical presentation, course of illness, and treatment response of younger patients with schizophrenia have been well-documented. Although there are some inconsistencies, women, in general, have been noted to have a later onset of illness, better response to neuroleptics, and better outcome. In terms of differences in clinical presentation, women have been reported to exhibit more affective symptoms, primarily related to depression, as well as more severe positive or paranoid symptoms. and less severe negative symptoms than men.

Gender differences have also been noted in neuroradiological and neurocognitive studies, but the results are inconsistent. Some researchers 10,11 have reported that men with schizophrenia have significantly larger ventricles relative to male comparison groups while women with schizophrenia do not differ from female comparison groups in this respect. In contrast, other studies¹² have reported that women with schizophrenia had significantly larger ventricles relative to those of female controls, whereas the ventricles in men with schizophrenia did not differ from those in male controls. In terms of gender differences in cognitive functioning, some researchers have noted that male schizophrenia patients performed worse than female patients, ^{13,14} while others have found that female patients had more impaired cognitive performance than male patients. 15 More recent studies of cognitive impairment in schizophrenia have reported no gender differences. 1,16,17

There is, to our knowledge, only one previous study of gender differences in older patients with psychosis.¹⁸ The results of that study investigating gender differences in elderly inpatients (over 65 years of age) with schizophrenia noted that men had more severe negative symptoms. There were no gender differences in terms of positive symptoms in this older patient sample, and depressive symptoms were not investigated.

In examining older patients with schizophrenia, we decided to address the issue of late-onset schizophrenia, as patients with late onset have been reported to manifest fewer negative symptoms, have a lower need for neuroleptics, and more commonly be women. ^{19–23} It is possible that some of the differences in the clinical presentation of late-onset compared with early-onset schizophrenia may relate to gender differences in the late-onset group only. Consequently, the interaction of age at onset and gender requires examination.

We hypothesized that there would be separate and joint effects of gender and age at onset on the clinical presentation of schizophrenia in older patients. Specifically, we hypothesized that older women with schizophrenia would have a later age at onset, more severe positive symptoms, less severe negative symptoms, and more depressive symptoms than men. Additionally, we conjectured that older patients with early-onset schizophrenia would have more severe negative and less severe positive symptoms than patients with late onset, regardless of gender. Furthermore, we hypothesized a joint effect of age at onset by gender, with late-onset women having more severe positive symptoms and less severe negative symptoms relative to women with early onset, men with late onset, and men with early onset. In addition to investigating age at onset as a dichotomous variable, we also wished to explore separately the degree of association between the age at onset of schizophrenia as a continuous variable and severity of negative symptoms, positive symptoms, and depression in women and men.

METHOD

Subjects

Outpatients (34 women and 90 men) with schizophrenia aged 46 to 85 years were recruited from the San Diego Veterans Affairs (VA) Medical Center, the University of California San Diego Medical Center and Psychiatry Outpatient Services, San Diego County Mental Health Services, and from private physicians. Parts of this data set have been analyzed previously with regard to clinical and neuropsychological characteristics of early-onset versus

late-onset schizophrenia patients. ^{21,22,24} The present study is the first, however, to focus on gender differences in this sample of patients over the age of 45 years. All of the subjects were physically and psychiatrically stable for at least 1 month prior to enrollment into the study. Diagnosis was made using the Structured Clinical Interview for the DSM-III-R or DSM-IV (SCID). ²⁵ To control for the potential differences in the response of negative symptoms to typical and atypical antipsychotics, patients who were receiving atypical antipsychotic medication were excluded from this study. Other exclusion criteria were diagnosable dementia, seizure disorder, history of head injury with unconsciousness for longer than 30 minutes, and current substance abuse or dependence meeting DSM-III-R ²⁶ or DSM-IV criteria. ²⁷

Clinical Evaluation

Relevant demographic and socioeconomic data, as well as extensive medical and pharmacologic histories, were obtained for each subject by interview and corroborated by information from medical records or a family member or both. A neurologic and physical examination was performed and appropriate laboratory evaluations were done as clinically indicated.

For the assessment of positive symptoms of schizophrema, the global score on the Scale for the Assessment of Positive Symptoms (SAPS)²⁸ was used, and negative symptoms were assessed with the global score on the Scale for the Assessment of Negative Symptoms (SANS).²⁹ The Brief Psychiatric Rating Scale (BPRS)³⁰ was used to assess overall psychopathology. For the assessment of depression, the Hamilton Rating Scale for Depression (HAM-D)³¹ was administered. The interrater reliability using the intraclass correlation coefficient (ICC) ranged from .86 to .92 for these scales (BPRS, ICC = .88; SAPS, ICC = .88; SANS, ICC = .86; HAM-D, ICC = .92). Further analyses were performed using the subscales of the SAPS and SANS, and the following subscales of the BPRS: positive symptoms (disorganized speech, hallucinatory behavior, and unusual thought content), negative symptoms (emotional withdrawal, motor retardation, and blunted affect), and depressive symptoms (anxiety statements, guilt feelings, and depressed mood). The Mini-Mental State Exam (MMSE)³² was used to measure global cognitive impairment. All the assessments were performed by raters blind to diagnosis, other clinical data, and study hypotheses. Age at onset of schizophrenia was defined as the age at which the individual reported experiencing prodromal symptoms. Late onset was defined per DSM-III-R, i.e., schizophrenia with an onset of prodromal symptoms after the age of 45 years.

Tabl	e 1.	Samp	le C	haracteristics a	nd	ANOV	/A]	Result	ts
------	------	------	------	------------------	----	------	-------------	--------	----

		men		Men				Statistical Test of Effects						
	EOS (N	= 20)	LOS (N	V = 14	EOS (N	N = 72	LOS (N	= 18)	G	ender	Age a	at Onset	Inte	raction
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p Value	F	p Value	F	p Value
Age (y)	59.2	11.5	65.5	9.1	59.1	9.3	63.1	6.8	0.20	.66	6.02	.02	0.32	.58
Education (y)	13.2	2.1	12.6	2.8	12.2	2.6	12.9	3.3	1.05	.31	0.15	.70	1.10	.30
MMSE total	26.7	3.5	27.2	2.5	27.0	2.9	26.9	2.5	0.03	.87	0.67	.41	0.13	.72
Daily neuroleptic	()													
dose ^{b,c} (mg CPZe	585	685	177	114	816	986	227	117	1.22	.27	6.10	.02	0.15	.70
Duration														
of illness (y)d	32,6	14.7	8.4	6.5	33.6	11.1	7.7	7.1	0.04	.85	122.76	.00	0.13	.72

^aAbbreviations: ANOVA = analysis of variance, CPZe= chlorpromazine equivalent, EOS = early-onset schizophrenia, LOS = late-onset

Table 2. Assessment Scale Scores and ANCOVA Results^a

				() \										
		W	omen	10		N.	Ien			Sta	tistical '	Test of Effe	ects	
	EOS (N	N = 20	LOS (N	(= 14)	EOS (N	J = 72	LOS (N	V = 18	Ge	nder	Age	at Onset	Inte	eraction
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p Value	F	p Value	F	p Value
SAPS total	7.6	4.7	6.4	3.8	5.6	(3.7)	5.4	4.1	4.48	.04	0.16	.69	0.33	.58
SANS total	8.3	4.4	4.1	2.3	8.4	4.5	7.8	3.2	1.98	.16	3.24	.07	4.07	.05
HAM-D total b,c	12.1	6.2	9.8	3.7	9.1	5.7	10.2	6.3	2.68	.10	0.03	.86	0.90	.34
BPRS total c	36.2	10.3	32.2	6.3	32.8	8.6	32.9	9.4	1.49	.26	0.14	.70	0.94	.33

^aCPZ equivalent used as the covariate (log transformed in analysis). Abbreviations: ANCOVA = analysis of covariance, BPRS = Brief Psychiatric Rating Scale, HAM-D = Hamilton Rating Scale for Depression, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

Statistical Methods

Transformations were performed when necessary so that the assumptions of normality were met for all the continuous variables (Tables 1 and 2). To examine overall gender differences in age, education, global cognitive status, daily neuroleptic dose, and duration of illness, 2-way (gender by age at onset) analyses of variance (ANOVA) were performed. Because the sample was dichotomized on age at onset (early onset vs. late onset), a t test was performed to investigate gender differences. Gender differences on categorical variables were analyzed using the chi-square statistic (Table 3).

The effects of gender, age at onset (early vs. late onset), and the interaction between these 2 variables were examined on the severity of positive, negative, and depressive symptoms in patients with late-onset and early-onset schizophrenia using a 2×2 (gender by age at onset) ANOVA. The effect of daily neuroleptic dose (mg chlor-promazine equivalents [CPZ equivalents]) on the clinical presentation was assessed by performing a 2×2 analysis of covariance (ANCOVA) with CPZ equivalents as the covariate. A similar analysis was performed on the BPRS

Table 3. Sample Characteristics and Chi-Square Results										
Variable	Women	Men	χ^2	p Value						
White, %	82.4	78.9	0.18	.67						
Late-onset schizophrenia, %	41.2	20.0	5.78	.02						
Paranoid subtype, %	67.6	56.7	1.24	.27						
Ever married, %	82.4	62.1	4.60	.03						
Taking neuroleptics, %	67.6	75.6	0.79	.37						

total score and subscales. Further information about the type of positive or negative symptoms was obtained by performing a 2-way ANCOVA for each subscale of the SAPS and SANS.

To address the relationship of age at onset as a continuous variable and the severity of positive (SAPS total score), negative (SANS total score), and depressive symptoms (HAM-D total score), Pearson product moment correlations were performed for the entire sample and separately for women and men.

An alpha of .05, 2-tailed, was used for the criterion of statistical significance. The SPSS statistical software package³³ was used for analyses.

 $schizophrenia,\ MMSE=Mini-Mental\ State\ Examination.$

Includes patients on neuroleptic only (women, N = 23; men, N = 68).

^cLog transformed in the analysis.

^dSquare root transformed in the analysis.

^bWomen, N = 30; men, N = 86.

^cSquare root transformed in the analysis.

RESULTS

The demographic and clinical characteristics of subjects are given in Tables 1 and 3. Women and men with schizophrenia were comparable in age, education, ethnicity, diagnostic subtype, duration of illness, and global cognitive status. The later age at onset of schizophrenia in women was statistically significant (t = 2.21, p = .03). There was no gender difference in the proportion of patients taking neuroleptics or in mean daily dose of CPZ equivalents, although women with schizophrenia did receive slightly lower doses. Women with schizophrenia were more likely to have been married and to have been classified as having late onset than were men.

As expected, patients with late-onset schizophrenia were significantly older, had a later age at onset of schizophrenia, and shorter duration of illness than those with early onset (see Table 1). Furthermore, patients with late onset received significantly lower doses of neuroleptics. There were, however, no significant interaction effects among these variables.

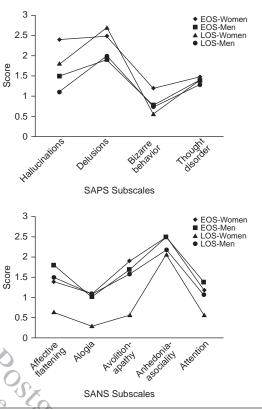
To address the effects of antipsychotic medication on symptom presentation and potential gender differences in response to neuroleptics, all analyses were performed with and without controlling for doses of CPZ equivalents. The relationship between CPZ equivalents and any of the dependent variables was not statistically significant, and very similar results were obtained for both the ANOVA and ANCOVA. We have reported, however, the significance values for the ANCOVA in Table 2.

In terms of gender differences in clinical presentation, women with schizophrenia had significantly more severe positive symptoms (SAPS total score) than men (see Table 2). There were no significant overall gender differences in terms of severity of negative symptoms (SANS total score), global psychopathology (BPRS total score), or the severity of depressive symptoms as measured by the HAM-D, although women with schizophrenia had significantly more severe symptoms on the depression subscale of the BPRS (F = 3.84, p < .05) than men.

There was a trend for older patients with early-onset schizophrenia to have more severe negative symptoms than comparably aged patients with late onset. The early-onset and late-onset groups, however, did not differ significantly on overall global psychopathology or positive or depressive symptoms on any of the scales or subscales assessed.

The age at onset by gender interaction was not significant for positive symptoms, overall global psychopathology, or depressive symptoms. Women with late-onset

Figure 1. Gender and Age at Onset Differences in SAPS and SANS Subscales



schizophrenia, however, had significantly lower total SANS scores relative to women with early onset, men with early onset, and men with late onset. There were no significant age at onset or interaction effects on the BPRS or its subscales.

Examination of the SAPS and SANS subscale scores revealed gender and gender by age at onset effects. Women had significantly more severe hallucinations and more severe delusions than men (F = 5.83, p < .05; F = 3.87, p < .05), whereas men with schizophrenia had significantly more affective flattening than women (F = 5.00, p < .05) (Figure 1). There was a significant gender by age at onset interaction for the alogia and avolition-apathy subscales of the SANS, with women with late onset having the lowest scores (F = 4.38, p < .05 and F = 4.74, p < .05, respectively).

When the data on men and women were combined, there was a significant correlation of age at onset of illness with severity of negative symptoms (SANS total score, r = -0.23, p < .01), but not with severity of positive symptoms (SAPS total score, r = 0.01) or depressive

symptoms (HAM-D total score, r=0.03). When the gender groups were considered separately, women with schizophrenia had a significant inverse correlation of severity of negative symptoms with age at onset (r=-0.41, p<.05). The correlation of severity of positive symptoms (r=0.13) and depressive symptoms (r=0.08) with age at onset of illness, however, failed to reach significance in women. In men, there was no significant correlation of age at onset with severity of positive symptoms (r=-0.11) or severity of negative symptoms (r=-0.11) or depressive symptoms (r=-0.01).

DISCUSSION

Sample Characteristics

Before discussing the results relevant to the specific hypotheses, it is worth noting that our older sample of patients with schizophrenia demonstrated many gender differences that have been observed in younger patients, although ours was a sample of convenience and not an epidemiologic sample. For example, in our sample, women with schizophrenia were more likely to have married and, consistently, were more likely to have received a diagnosis of late-onset schizophrenia than men. In contrast with previous findings in younger patients, we did not find gender differences in the proportion of patients on neuroleptic medication or in daily dose of neuroleptic as measured by CPZ equivalents. The gender difference in age at onset is consistent with previous findings of later age at onset in women. 4,19,34-36 The greater proportion of women with late onset than men has also been found in other studies.³⁷ Age at onset of schizophrenia also most likely accounts for the significant gender differences we observed between men and women in terms of the likelihood of having married, with women benefiting from the longer period of better premorbid functioning. We failed to find the gender difference that we predicted in the amount of daily neuroleptic dose between men and women in this sample of older patients with schizophrenia. Several possibilities could account for this finding. The lower dose of antipsychotic medication that is usually prescribed for older patients may have resulted in an attenuation of the gender differences. Examination of the means in this sample did, however, suggest that women were receiving lower doses of neuroleptics.

Hypothesis Testing

We confirmed our hypothesis that women would have more severe positive symptoms, but failed to confirm our hypothesis that women would have less severe negative symptoms. However, women with late-onset schizophrenia had significantly less severe negative symptoms than women with early onset or men with late onset or early onset. Furthermore, age at onset of schizophrenia was inversely correlated with severity of negative symptoms for women but not for men. These results suggest that age at onset (early onset or late onset) interacts with gender to influence the clinical presentation of schizophrenia.

We also confirmed the hypothesis that older women with schizophrenia had significantly more severe positive symptoms than men, specifically more severe delusions and hallucinations. More positive symptoms in women with schizophrenia have been reported in a number of studies. ⁶⁻⁸

In contrast to previous reports, 4,6,38 we did not confirm the hypothesis that women had more depressive symptoms as measured by the HAM-D, although we did find that women had higher depressive subscale scores on the BPRS than did men. In the previous studies, the method of measuring depression either was not stated or was measured by individual items. The discrepancy between the HAM-D and the subscale of the BPRS in this study, as well as the inconsistent results of other studies, might be due to the differences among the scales in the measurement of depression. The construct of depression is multifaceted (e.g., somatic, behavioral, mood, and cognitive aspects), and depression scales may also measure other related domains of psychopathology (for example, the subscale of the BPRS employed in this study contained an item pertaining to anxiety). The nature of depression in schizophrenia warrants further investigation.

As predicted, there was a trend for early-onset patients to have more severe negative symptoms, but the early-onset and late-onset groups did not differ with regard to positive symptoms. Many studies have reported an increase in negative symptoms and a decrease of positive symptoms with longer duration of illness. ¹⁸ Given the shorter duration of the late-onset group, it is not surprising that we found no age at onset differences for positive symptoms. The results of this study showed that negative symptom severity in men with late-onset schizophrenia was the same as that in men with early onset, yet women with late onset had significantly less severe negative symptoms, and specifically less alogia, avolition, and apathy.

These results also have implications for our understanding of late-onset schizophrenia. Previous studies have reported a greater proportion of women, as well as more severe positive and less severe negative symptoms, in this group compared with early-onset schizophrenia. In

terms of the relationship between age at onset and psychopathology, we confirmed our hypothesis that there would be a significant relationship between age at onset of illness and severity of negative symptoms, but this relationship was observed only in women. In men, there was no significant relationship between age at onset and severity of positive, negative, or depressive symptoms. Taken together, these results suggest that some of the clinical differences between late-onset and early-onset schizophrenia may be related to gender effects.

To summarize, we found an overall increase in the severity of positive symptoms in women with schizophrenia, a greater proportion of women than men being classified as late onset, and less severe negative symptoms observed in women with late onset. We concluded that there are at least 3 possibilities to explain these results. One explanation is that women and men have the same type of schizophrenia, but that women demonstrate a milder form with a later onset, a prolonged period of premorbid functioning, less severe psychotic symptoms, and perhaps a better response to neuroleptics. If this were the case, however, women with early onset should also have less severe negative symptoms compared with men with early onset, a finding that is inconsistent with our results. Furthermore, we found that women with schizophrenia, including women with late onset, had more severe positive symptoms (hallucinations and delusions).

The second explanation that might account for our results is that estrogen may act as a "protective factor." The loss of estrogen after menopause could result in the appearance of schizophrenia for the first time in women. Several researchers have proposed that estrogen may have an antipsychotic effect, and several lines of evidence from animal and human studies suggest that estradiol acts as a dopamine antagonist. Thus, the increase in dopaminergic tone as a result of a loss of estrogen would be predicted to result in greater positive symptoms in women regardless of age at onset, and perhaps unmask schizophrenia that presents for the first time postmenopausally. This explanation, however, does not account for the less severe negative symptoms found in women with lateonset schizophrenia.

A third possibility to explain both the increased percentage of women with late onset compared with men, and why women with late onset have fewer negative symptoms than any of the other patient groups, is that menopause may allow for the emergence of a different type of schizophrenia, one that is masked by the presence of estrogen and characterized by fewer negative symptoms. If there is such an "estrogen-related" schizophrenia,

it would likely only be obvious in women, because men have low levels of estrogen throughout their life span, and therefore an estrogen-related schizophrenia would emerge early in life in men and be difficult to identify from among the other forms of schizophrenia presenting at approximately the same age. Such an estrogen-related schizophrenia might be expected to exhibit clinical improvement in response to estrogen administration, and we are currently engaged in studies to test this hypothesis.

Limitations

There are several limitations to our study. The relationships of age, gender, and subtype to various neuropsychiatric variables may be different among more severely ill patients than among the stable outpatients in this study. Secondly, the cross-sectional design of this study precludes drawing any conclusions about the course of positive and negative symptoms or gender-related differences in response to antipsychotics over time. Longitudinal studies are needed to clarify issues related to gender differences in the course of symptoms.

In conclusion, our results suggest that, as in younger patients, middle-aged and elderly women with schizophrenia have more severe positive psychotic symptoms than men. Also, in women alone, older age at onset was associated with fewer negative symptoms, whereas older men with schizophrenia have approximately the same level of severity of negative symptoms regardless of age at onset. These gender-associated differences may relate to clinical differences observed between late-onset schizophrenia and early-onset schizophrenia and may also relate to the occurrence of menopause. Whether the clinical presentation specific to women with late-onset schizophrenia represents a modification of the symptoms of schizophrenia or the existence of different subtype of schizophrenia warrants further investigation.

Drug name: chlorpromazine (Thorazine and others)

REFERENCES

- Andia AM, Zisook S, Heaton RK, et al. Gender differences in schizophrenia. J Nerv Ment Dis 1995;183:522–528
- Szymanski S, Lieberman JA, Alvir JM, et al. Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. Am J Psychiatry 1995;152:698–703
- Shtasel DL, Gur RE, Gallacher F, et al. Gender differences in the clinical expression of schizophrenia. Schizophr Res 1992;7:225–231
- Lewine R. Sex differences in schizophrenia: timing or subtype? Psychol Bull 1981;90:432–444
- Lewine R. Schizophrenia: an amotivational syndrome in men. Can J Psychiatry 1985;30:316–318
- Goldstein JM, Link BG. Gender and the expression of schizophrenia. J Psychiatr Res 1988;2:141–155

CME: ARTICLE

- Castle DJ, Sham PC, Wessely S, et al. The subtyping of schizophrenia in men and women: a latent class analysis. Psychol Med 1994;24:41–51
- Marneros A. Frequency of occurrence of Schneider's first rank symptoms in schizophrenia. Eur Arch Psychiatry Neurol Sci 1984;234:78–82
- Goldstein JM, Santangelo SL, Simpson JC, et al. The role of gender in identifying subtypes of schizophrenia: a latent class analytic approach. Schizophr Bull 1990;16:263–275
- Flaum M, Arndt S, Andreasen NC. The role of gender in studies of ventricle enlargement in schizophrenia: a predominantly male effect. Am J Psychiatry 1990;147:1327–1332
- Nopoulos P, Flaum M, Andreasen NC. Sex differences in brain morphology in schizophrenia. Am J Psychiatry 1997;154:1648–1654
- Nasrallah H, Schwarzkopf S, Olson S, et al. Gender differences in schizophrenia on MRI brain scans. Schizophr Bull 1990;16:205–210
- The Scottish Schizophrenia Research Group. The Scottish first episode study, III: cognitive performance. Br J Psychiatry 1987;150:338–340
- Aylward E, Walker É, Bettes B. Intelligence in schizophrenia: meta-analysis of the research. Schizophr Bull 1984;10:430–459
- Perlick D, Mattis S, Stastny P, et al. Gender differences in cognition in schizophrenia. Schizophr Res 1992;8:69–73
- Goldberg TE, Gold JM, Torrey EF, et al. Lack of sex differences in the neuropsychological performance of patients with schizophrenia. Am J Psychiatry 1995;152:883–888
- Albus M, Hubmann W, Mohr F, et al. Are there gender differences in neuropsychological performance in patients with first-episode schizophrenia? Schizophr Res 1997;28:39–50
- Arnold SE, Gur RE, Shapiro RM, et al. Prospective climicopathologic studies of schizophrenia: accrual and assessment of patients. Am J Psychiatry 1995;152:731–737
- Harris MJ, Jeste DV. Late-onset schizophrenia: an overview. Schizophr Bull 1988:14:39–55
- Pearlson G, Rabins P. The late-onset psychoses: possible risk factors. In: Jeste DV, Zisook S, eds. The Psychiatric Clinics of North America: Psychosis and Depression in the Elderly. Philadelphia, Pa: WB Saunders Co; 1988:15–32
- Jeste DV, Harris MJ, Krull A, et al. Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. Am J Psychiatry 1995;152:722–730
- Jeste DV, Symonds LL, Harris MJ, et al. Non-dementia non-praecox dementia praecox? late-onset schizophrenia. Am J Geriatr Psychiatry 1997;5:302–317
- Riecher-Rossler A, Loffler W, Munk-Jorgensen P. What do we really know about late-onset schizophrenia? Eur Arch Psychiatry Clin Neurosci 1997;247:195–208
- Heaton R, Paulsen J, McAdams LA, et al. Neuropsychological deficits in schizophrenia: relationship to age, chronicity and dementia. Arch Gen Psychiatry 1994;51:469–476
- Spitzer RL, Williams JBW, Gibbon M, et al. User's Guide for the Structured Clinical Interview for DSM-III-R. Washington, DC: American Psychiatric Press; 1990
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Press: 1987

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
- Andreasen NC, Olsen S. Negative vs positive schizophrenia: definition and validation. Arch Gen Psychiatry 1982;39:789–794
- Andreasen NC. The Scale for the Assessment of Negative Symptoms in Schizophrenia (SANS). Iowa City, Ia: University of Iowa; 1983
- Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962:10:799–812
- Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
- Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
- Norusis MJ. SPSS/PC+ Statistical Software, V2.0. Chicago, Ill: SPSS Inc; 1988
- Loranger AW. Sex difference in age at onset of schizophrenia. Arch Gen Psychiatry 1984;41:157–161
- Castle DJ, Murray RM. The epidemiology of late-onset schizophrenia. Schizophr Bull 1993;19:691–700
- Hafner H, Maurer K, Loffler W, et al. The influence of age and sex on the onset and early course of schizophrenia. Br J Psychiatry 1993;162:80–86
- Mattson RH, Calverly JR. Dextroamphetamine, sulfate, induced dyskinesias. JAMA 1968;204:108–110
- Westermeyer JF, Harrow M. Prognosis and outcome using broad (DSM-II) and narrow (DSM-III) concepts of schizophrenia. Schizophr Bull 1984;10:624

 –637
- Seeman MV, Lang M. The role of estrogens in schizophrenia gender differences. Schizophr Bull 1990;16:185–194
- 40. Riecher-Rossler A, Hafner H, Stumbalum M, et al. Can estradiol modulate schizophrenic symptomatology? Schizophr Bull 1994;20:203–213
- Riecher-Rossler A, Hafner H, Dutsch-Strobel A, et al. Further evidence for a specific role of estradiol in schizophrenia. Biol Psychiatry 1994;36: 492–495
- Riccher-Rossler A, Rossler W, Forstl H, et al. Late-onset schizophrenia and late paraphrenia. Schizophr Bull 1995;21:345–354
- Di Paolo T, Bedard PJ, Dupont A, et al. Effects of estradiol on intact and denervated striatal dopamine receptors and on dopamine levels: a biochemical and behavioral study. Can J Physiol Pharmacol 1996;60: 350–357
- Bedard P, Boucher R, Di Paolo T, et al. Biphasic effect of estradiol and domperidone on lingual dyskinesia in monkeys. Exp Neurol 1983;82: 172–182

DISCLOSURE OF OFF-LABEL USAGE

The faculty of this activity have determined that, to the best of their clinical estimation, no investigational information about pharmaceutical agents has been presented herein that is outside Food and Drug Administration—approved labeling.

Instructions

Psychiatrists may receive 1 hour of Category 1 credit toward the American Medical Association Physician's Recognition Award by reading the article starting on page 61 and correctly answering at least 70% of the questions in the posttest that follows.

- 1. Read each question carefully and circle the correct corresponding answer on the Registration form.
- 2. Type or print your full name, address, Social Security. phone, and fax numbers in the spaces provided.
- 3. Mail the Registration form along with a check, money order, or credit card payment in the amount of \$10 to: Physicians Postgraduate Press, Office of CME, P.O. Box 752870, Memphis, TN 38175-2870.

4. For credit to be received, answers must be postmarked by the deadline shown on the CME Registration form. After that date, correct answers to the posttest will be printed in the next issue of the Journal.

All replies and results are confidential. Answer sheets, once graded, will not be returned. Unanswered questions will be considered incorrect and so scored. Your exact score can be ascertained by comparing your answers with the correct answers to the posttest, which will be printed in the Journal issue after the submission deadline. The Physicians Postgraduate Press Office of Continuing Medical Education will keep only a record of participation, which indicates the completion of the activity and the designated number of Category 1 credit hours that have been awarded.

1. Relative to men with schizophrenia, women with schizophrenia have:

- a. More severe negative symptoms
- b. More severe positive symptoms
- c. A similar clinical presentation
- d. Less severe negative symptoms
- e. Less severe positive symptoms

2. Patients with late-onset schizophrenia:

- a. Have more severe negative than positive symptoms
- b. Have more severe negative symptoms than younger patients
- c. Are more likely to be men
- d. Are more likely to be women
- e. Have more severe negative and positive symptoms than younger patients

3. In women only, age at onset of schizophrenia is associated with:

- a. Negative symptoms
- b. Positive symptoms
- c. Depressive symptoms
- d. Negative and positive symptoms
- e. Negative, positive, and depressive symptoms

4. Estrogen may influence the onset and clinical presentation of schizophrenia by:

- a. Facilitating dopamine transmission
- b. Inhibiting dopamine transmission
- c. Facilitating norepinephrine transmission
- d. Inhibiting norepinephrine transmission
- e. None of the above

5. It is not possible to draw conclusions about gender differences in the course of schizophrenia from this study because:

- a. The sample consists of outpatients
- b. No younger patients were ...

 c. It is a cross-sectional study

 d fris a longitudinal study

 in too smal b. No younger patients were included
- e. It is a cross-secuonal study
 d. It is a longitudinal study
 e. The sample size is too small

6. It can be concluded from this study that:

- a. Gender alone affects the clinical presentation of schizophrenia
- b. Age alone affects the clinical presentation of schizophrenia
- c. Age at onset alone affects the clinical presentation of schizophrenia
- d. Gender and age at onset interact to affect the clinical presentation of schizophrenia
- e. Nothing can be concluded

7. Age at onset and gender are important to consider together in understanding the clinical presentation of schizophrenia because:

- a. They may affect the severity of negative symptoms
- They may affect the severity of positive symptoms
- c. They may affect the severity of depressive symptoms
- They may influence severity of overall psychopathology
- e. They may influence severity of cognitive impairment

Answers to the July 1998 CME posttest

2. d 3. a 4. a 5. e 6. c 7. a

CME: REGISTRATION/EVALUATION

Circle the o	ne correct	answer	for eac	h quest	ion.	Please evaluate the effectiveness of this CME activity l						
1.	a	b	c	d	e	answering the following questions.						
2.	a	b	c	d	e	1. Was the educational content relevant to the stated						
3.	a	b	c	d	e	educational objectives? \(\subseteq \text{Yes} \subseteq \text{No} \)						
4.	a	b	c	d	e	2. Did this activity provide information that is useful in your						
5.	a	b	c	d	e	clinical practice? \(\text{\texts} \) Yes \(\text{\texts} \) No						
6.	a	b	c	d	e	2 Wester Court of this artist and a contract of the contract						
7.	a	b	С	d	e	3. Was the format of this activity appropriate for the content being presented? ☐ Yes ☐ No						
Print or typ Name						4. Did the method of presentation hold your interest and make the material easy to understand? ☐ Yes ☐ No						
						· -						
(for CME credit r						5. Achievement of educational objectives:						
_		_	-			A. Enabled me to consider how gender differences in olde patients may affect the clinical presentation of schizophrenia. \(\subseteq\) Yes \(\supseteq\) No						
Address						B. Enabled me to examine how age at onset and gender						
-	_					may interact in the clinical presentation of schizophrenia in geriatric patients. \(\sqrt{Yes} \sqrt{No} \) No						
						-						
						6. Did this CME activity provide a balanced, scientifically rigorous presentation of therapeutic options related to th topic, without commercial bias? ☐ Yes ☐ No						
Hospital: 🗖	Private F	Practice:	□ Re	esident:	☐ Intern: ☐	·]						
no later than	to be recei June 30, 19	999 (outs			oe postmarked ntal United	7. Does the information you received from this CME activity confirm the way you presently manage your patients? ☐ Yes ☐ No						
States, Augus	st 31, 1999)).				8. Does the information you received from this CME activity						
	copy of you	r answei			hem with the	change the way you will manage your patients in the future? \square Yes \square No						
deadline.	ers, which	wiii be p	ublished	i arter til	ie subillission	9. Please offer comments and/or suggested topics for future						
Payment A \$10 pay	ment must	accomp	any this	form. Y	ou may pay b	CME activities.						
check, mone	y order, or oney order p	credit ca ayable to	rd (Visa Physic	or Mast ians Pos	terCard). Mak							
Check one:	☐ Visa	☐ Mas	sterCar	d								
Card number	er					10. How much time did you spend completing this CME						
Expiration of	date											
Your signat	ure											

Tear out and mail this page, along with your payment, to:
Physicians Postgraduate Press • Office of Continuing Medical Education • P.O. Box 752870 • Memphis, TN 38175-2870

If you are paying by credit card, you may fax this page to: Office of Continuing Medical Education at 901-751-3444