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Is Late-Onset Schizophrenia a Subtype of Schizophrenia?

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Abstract

Objective—To determine whether late-onset schizophrenia (LOS, onset after age 40) should be considered a distinct subtype of schizophrenia.

Method—Participants included 359 normal comparison subjects (NCs) and 854 schizophrenia outpatients age > 40 (110 LOS, 744 early-onset schizophrenia or EOS). Assessments included standardized measures of psychopathology, neurocognition, and functioning.

Results—EOS and LOS groups differed from NCs on all measures of psychopathology and functioning, and most cognitive tests. EOS and LOS groups had similar education, severity of depressive, negative, and deficit symptoms, crystallized knowledge, and auditory working memory, but LOS patients included more women and married individuals, had less severe positive symptoms and general psychopathology, and better processing speed, abstraction, verbal memory, and everyday functioning, and were on lower antipsychotic doses. Most EOS-LOS differences remained significant after adjusting for age, gender, severity of negative or deficit symptoms, and duration of illness.

Conclusions—LOS should be considered a subtype of schizophrenia.

Keywords

Schizophrenia; aging; cognition; negative symptoms; quality of life; positive symptoms

> "…more than two-thirds of the cases [of dementia praecox] begin between the fifteenth and thirtieth year…However, there can be no talk of an inviolable connection of dementia praecox with the period of youth… a not inconsiderable number of cases still reach development in the fourth, fifth, and even in the sixth decade"
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> Emil Kraepelin, 1913 (1)

INTRODUCTION

Over the past century there has been considerable debate regarding late-onset schizophrenia (LOS) (2–6). The roots of this debate were present at the close of the 19th century when Kraepelin conceptualized and labeled schizophrenia as *dementia praecox* (referring to

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mental decline starting at a precocious age) (7,8). Kraepelin's terminology proved controversial (9). As illustrated by the above quote, by 1913 Kraepelin himself abandoned the notion that the onset of this disorder was restricted to adolescence and early adulthood. As Kraepelin (1) and Eugen Bleuler (10) were still actively delineating dementia praecox/schizophrenia from affective psychoses, there were a number of reports in the German literature of schizophrenia-like syndromes with mid- or late-life onset (11). Larger-scale systematic investigation began in the 1940's with the work of Manfred Bleuler (12), who coined the term "spätschizophrenie" ("late schizophrenia") to describe persons whose symptoms first manifested after age 40 (11). Excluding individuals whose symptoms might be attributed to amnestic or other neurologic or medical conditions, Manfred Bleuler observed that approximately 15% of schizophrenia patients manifested onset of symptoms after age 40.

Systematic studies of LOS (with onset after age 40) continued in Germany (11,13). In other European countries (especially UK) there were scholarly reports in the 1950s and 1960s of patients with very-late onset (often age 60 or older) psychoses that were described with labels such as "late paraphrenia" (14–16), "persistent persecutory states" (17,18), or "senile schizophrenia" (19). Late-onset psychoses were virtually ignored in American psychiatry until the 1980s (20), but the term "late paraphrenia" gained some traction in Europe and Japan (21,22).

As noted in a review of the literature by Riecher-Rössler, Häfner, & Munk-Jørgensen (23), methodological limitations plagued definitive interpretation and comparison of results from studies of LOS, late paraphrenia, and similar conditions. In addition to inconsistencies in diagnostic terminology and criteria (15,19,22,24), a key methodological problem was use of divergent age cut-offs for what constituted "late onset" (10,14,16,25,26). Whereas LOS, as invested by Manfred Bleuler and subsequent German researchers generally focused on those with onset between ages 40 and 60, studies of late paraphrenia and related psychoses in the UK and elsewhere often focused on persons with onset after age 50, 60, or 65 years. The term "late paraphrenia" was sometimes used as a synonym for LOS but others employed it to describe a more circumscribed paranoid psychosis similar to paraphrenia (without reference to age of onset) that Kraepelin (1) had delineated in 1913 (23,27).

In order to bring greater consistency to the study and clinical recognition/treatment of late-onset psychotic disorders, an international conference was held in 1998, attended by experts in late-life schizophrenia from 12 different countries. This conference resulted in a consensus statement which concluded that LOS, with onset of prodromal symptoms after age 40, had at least face validity (2). The diagnostic label for persons whose symptoms emerged after age 60 was "very-late onset schizophrenia-like psychosis," reflecting less certainty about the nature of schizophrenia-like symptoms when they manifested at an age at which risk of primary dementias begins to increase. The recommendation to designate LOS as a formal subtype was not incorporated into either the ICD-10 (28) or DSM-IV-TR (29,30). The term "paraphrenia (late)" had been present under "paranoid states" in some earlier editions of the ICD; it was dropped from the initial draft of ICD-10, but that deletion generated controversy so it was added in the final version of ICD-10 but only as a part of "delusional disorder" rather than as a type of LOS (13). As planning progresses for the development of the ICD-11 and DSM-V, now appears an opportune time to consider available empirical data to address the question: Should LOS be considered a formal subtype of schizophrenia?

Implicit in the above question is the issue of what basis any subtyping should be proposed. The present subtyping of schizophrenia is largely based on phenomenology and historical concepts. Most of the schizophrenia subtypes in the ICD-10 (28) and DSM-IV-TR (30)

directly parallel subtype distinctions (paranoid, catatonic, undifferentiated, etc.) suggested a century ago by Kraepelin (1) and Bleuler (10). There is little empirical support or clinical utility of these phenomenology-based subtypes. In contrast, age of illness onset has been used to subtype medical disorders such as diabetes mellitus (31), Huntington's disease (32), and Alzheimer's disease (33) in a more useful manner. It has also been used to subtype other serious mental illnesses such as depression (34). Early-onset subtypes generally have worse course and outcome than late-onset ones, and also differ in biology (when it is known). Clinically, the distinction between early- versus late-onset illness may be particularly critical for schizophrenia because, when the illness emerges in adolescence or early adulthood, many of the normal psychosocial developmental tasks are interrupted. When the onset is delayed until mid-life, functional skills needed to survive in the adult-world are likely to be better established and ingrained. An optimal way to subtype a disorder should be based on its underlying etiology or at least known pathophysiology (35); however, despite advances in research (36,37), there are presently no proven biomarkers of schizophrenia (38), let alone its subtypes. Therefore, clinical relevance becomes the main criterion for subtyping schizophrenia.

Paralleling the historical lack of research attention to LOS that characterized American psychiatry until the 1980s (20,39), most of the contemporary published research on LOS originates from outside North America. We searched the PubMed database for articles published between January 1, 2004 and August 18, 2009; of 18 citations, 6 were published in non-English language journals; of the remaining 12, only one originated from the US (40), whereas four came, at least in part, from UK (41–44), three from Germany (45–47), one from Greece (48), one from France (49), one from Israel (50), and one from Brazil (51). Over the past two decades our research group at the University of California, San Diego (UCSD) has been systematically studying middle-aged and older patients with schizophrenia, as well as normal comparison subjects (NC). We have gathered a large dataset with comprehensive demographic, clinical, neurocognitive, and functioning data. The analyses conducted for the current study were designed to help address the question of whether older adults with LOS present with sufficient differences from those with EOS to warrant distinction of LOS as a formal schizophrenia subtype. We have published data from several smaller studies comparing EOS and LOS patients (25,52–55); however, the present report represents the first attempt to examine the combined data on LOS and EOS patients, and NCs, collected over the past two decades in our research program funded by the U.S. National Institute of Mental Health (NIMH). We evaluated the issue of LOS as a subtype of schizophrenia from three perspectives.

1. We postulated that, as LOS is a form of schizophrenia, the LOS and EOS groups would be similar to each other and different from NCs on several core characteristics of schizophrenia. Based on the larger literature showing the association of schizophrenia with not only psychopathology, but also with cognitive impairment and functional disability (56), we hypothesized that the LOS and EOS groups would have greater level of psychopathology, cognitive impairment, and functional disability than NCs. (Although our primary focus was on the similarities and differences between EOS and LOS patients, it was thought to be important to show first that the LOS group differed from the NCs in all critical dimensions.)

2. Based on the existing empirical literature (albeit of studies with much smaller sample sizes (2), we hypothesized that LOS would differ from EOS on several relevant characteristics – i.e., gender, psychopathology, cognitive impairment, everyday functioning, and antipsychotic dosages. For example, observations going back to the early 20th century (e.g., see Eugen Bleuler (10) pp. 341–342) suggest that the LOS group would have a higher proportion of women than the EOS group.

Similarly, based on prior studies of psychopathology in LOS and EOS, we hypothesized that LOS patients would have less severe overall psychopathology (57). Early-onset forms of illness tend to have worse course and outcome than later-onset variants (31–33). Accordingly, we postulated that LOS would be associated with less severe impairment in neurocognitive performance (especially executive functions). Given the reported importance of executive functions to independent functioning (58), we also hypothesized that LOS patients would have less severe impairment in everyday functioning than EOS patients. Finally, as noted by Howard et al. (2) open label observations suggest that LOS patients may be effectively managed on antipsychotic doses that are only about 40% as high as those needed with younger patients. Thus, we hypothesized that the mean daily dose of antipsychotic medications among LOS patients would be lower than that among EOS patients.

3. A potential counter-explanation for EOS-LOS differences is that these may be epiphenomena secondary to differences in some other primary characteristic(s) such as age, gender, negative symptoms, deficit syndrome, or duration of illness,. For example, Carpenter and colleagues have described the concept of Deficit Syndrome schizophrenia (59,60), characterized by insidious onset, worse neurocognitive functioning, and greater familial risk of schizophrenia (60–62). If Deficit Syndrome disproportionately manifests in a subset of patients with EOS relative to its prevalence among LOS patients, it might imply that the key distinction driving the EOS-LOS differences may be an over-representation of Deficit Syndrome among patients with EOS. According to this view, among the non-Deficit Syndrome patients with schizophrenia, there may be no systematic EOS-LOS differences. Similarly, although most longitudinal research indicates that cognitive deficits remain relatively stable throughout the post-onset course of schizophrenia (55,63,64), a few studies suggest that longer disease duration may be associated with worse executive functions and/or episodic declarative memory (65–67). On the other hand, based on the prior conclusions from the International Consensus Statement (2) that LOS warrants designation as a formal subtype, we hypothesized that the EOS-LOS differences in psychopathology, cognitive impairment, and everyday functioning would remain significant after adjusting for differences in age- and gender-corrected scores on severity of negative symptoms and of (a validated Proxy for) deficit syndrome, as well as after adjusting for duration of illness.

METHODS

Participants

The sample consisted of persons age > 40 years including 359 NCs, 744 individuals with EOS (age at first manifestation of prodromal symptoms < 40 years), and 110 with LOS (age at first manifestation of prodromal symptoms ≥ 40 years). Data were collected between August 1987 and July 2008, as a part of studies conducted through an NIMH-funded research program at UCSD. Recruitment sources included the UCSD and Veterans Affairs San Diego Healthcare System psychiatry services, the San Diego County Adult and Older Adult Mental Health Services, assisted living facilities in San Diego metropolitan region, as well as private practitioners.

Although the present report focuses on baseline data, many of the patients were reevaluated on an annual basis as part of longitudinal studies in our Research Center; among those, 93 % evidenced no subsequent change in the diagnosis of schizophrenia in either EOS or LOS group. Where a diagnostic change did occur, it involved bipolar disorder (7 patients with

EOS and 0 with LOS), depressive disorder (4 EOS and 3 LOS), and other conditions (2 EOS and 1 LOS).

Selection criteria—Inclusion criteria were: (1) DSM-III-R, DSM–IV diagnosis of schizophrenia or schizoaffective disorder, and no major psychiatric diagnosis for NCs, (2) current age > 40 years, and (3) English fluency. Exclusion criteria were: (1) presence of DMS-III-R or DSM–IV diagnosis of alcohol or other substance use disorder within 3 months preceding enrollment, (2) DSM-III-R or –IV diagnosis of dementia, or (3) presence or history of major neurological or other medical conditions likely to affect current cognitive functioning. All the subjects who met these criteria and had valid information on age of onset of illness and Positive And Negative Syndrome Scale (PANSS) (68) were selected for this study. The NCs were recruited via flyers, advertisements in local papers and newsletters, and word of mouth.

The research was approved by the UCSD Human Research Protections Program, and a written informed consent was obtained from all the participants.

Measures

Demographic characteristics—Age, education, gender, self-identified ethnic background, and current as well as past marital status were determined via interview and/or review of available records.

Clinical characteristics and motor symptoms—Age of onset of prodromal symptoms, duration of illness, and current antipsychotic medications (type and current daily antipsychotic dosage in mg chlorpromazine equivalent (CPZE) (69) were determined though patient or collateral interview, and/or review of available records. Severity of dyskinesia and other abnormal involuntary movements was determined with the Abnormal Involuntary Movement Scale (AIMS) (70).

Psychopathology—Severity of positive, negative, and general psychopathologic symptoms was measured with the respective subscales of the PANSS (68). Severity of depressive symptoms was measured with the 17-item Hamilton Rating Scale for Depression (HAM-D) (71).

Deficit syndrome: Based on the select items from the PANSS we also calculated the Proxy for Deficit Syndrome (or PDS) (72) score for each participant, i.e.:

$$PDS = BluntedAffect_{N1} - \left[Anxiety_{G2} + GuiltFeelings_{G3} + DepressedMood_{G6} + Hostility_{P7} \right]$$

The PDS was developed by the same investigators who originally proposed the concept of Deficit Syndrome, and has proved to be adequately sensitive and specific to Deficit Syndrome as defined by more comprehensive structured interview (72,73). As each of the PANSS items is scored on a 7 point scale: 1 (absent) to 7 (severe), the PDS has a potential range of −27 to +3; scores toward the positive range tend to be more strongly predictive of presence of Deficit Syndrome (72,73). We categorized each patient with schizophrenia as having “Deficit Syndrome” or “no Deficit Syndrome” using the originally published cut-point (PDS ≥ −2 defining Deficit Syndrome status) (72). However, as that cut-off has not been validated for use with an older adult sample such as ours, we also compared the study groups treating PDS total as a continuous variable.

Cognitive Performance—Subjects were assessed with a comprehensive neurocognitive test battery, including the Information, Vocabulary, Similarities, Picture Arrangement, Block Design, mental Arithmetic, and Digit Symbol subtests from the 1981 or 1997 versions of the Wechsler Adult Intelligence Scale (WAIS-R or WAIS-III) (74,75). Factor analyses suggest that these subtests measure many of the abilities key to characterizing cognitive status, including crystallized verbal knowledge (Information, Vocabulary, Similarities), perceptual-organization (Picture Completion, Block Design), auditory working memory (mental Arithmetic), and processing speed (Digit Symbol) (76,77). We also used perseverative response scores from the 128- or 64-card versions of the Wisconsin Card Sorting Test (WCST) (78,79) to assess abstraction/cognitive flexibility. Verbal memory was measured with the long-delay free recall score, adjusted for performance on the last learning trial (Trial 5), of the California Verbal Learning Test (CVLT) (80). Raw scores from the WAIS-R or WAIS-III and CVLT were expressed as Scaled Scores (normative mean 10, SD = 3). (Scores provided in the Results below are expressed in terms of the WAIS/WAIS-R "Reference Group" norms.) The WCST preservative response scores were expressed as T-scores (normative mean = 50, SD = 10) using the published census matched norms (78,79).

Everyday Functioning—Functioning measures included the UCSD Performance-based Skills Assessment (UPSA) (81) and the Social Skills Performance Assessment (SSPA) (82). Health-related quality of life was measured with the Quality of Well-Being (QWB) scale (83).

Procedures: For data collected in the initial years of the study, diagnoses were established with the Structured Clinical Interview for DSM-III-R or DSM-IV (SCID) (84,85), conducted by trained MD or PhD postdoctoral fellows, with diagnostic confirmation provided by a board-certified geriatric psychiatrist based on the information collected through the SCID. In general, there was a high correspondence between chart diagnoses and SCID-based diagnoses. In later years, diagnoses were established by the treating clinicians using DSM-IV or DSM-IV-TR criteria. We have previously reported on reliability of determination of age of onset of illness in our research (25). All other assessments were administered individually by trained bachelors-level research assistants (RAs). To avoid participant fatigue, the evaluations were completed over two or three days, as appropriate. Interrater reliability for the AIMS, PANSS, and HAM-D was regularly established for studies in our research center by having each RA rate videotaped interviews, and his/her ratings then compared to those of criterion standard by established investigators; training was continued until each RA achieved Intra-class Correlation Coefficients relative to the criterion standard of ≥ 0.80; this training was repeated annually to diminish rater drift. Cognitive and functioning measures were also administered by trained RAs; appropriate investigators and/or experienced postdoctoral fellows in neuropsychology met with the RAs on a regular basis to foster consistency in administration and scoring.

Statistical analyses

For categorical variables, the groups were compared using Pearson's Chi-square tests. For continuous variables Welsh's robust analysis of variance was used due to significantly unequal variances between the NC group and the patient groups. T-tests were used for pairwise comparisons. Due to significant age and gender differences among the groups, each of the outcome variables was replaced with a standardized age- and gender- corrected version. The latter values were obtained by first fitting linear regression models in the EOS group with each outcome variable as a dependant measure, and age, age-squared, and gender as predictors. From these models, standardized residuals for all the subjects were calculated and employed as age- and gender- corrected outcomes. To control for possible confounding influence of group differences in severity of negative symptoms and of deficit syndrome

(with PDS scores treated as a continuous variable), as well as differences in duration of illness, we also conducted additional analyses to adjust for these variables. Two-way analyses of variance (ANOVAs) were performed, including one confounder and one outcome variable in the model at a time. To avoid making strict assumptions about the linearity of the relationship between confounders and the outcome, the confounders were stratified into dummy variables for the analysis. Both variables were stratified into bins of the size of one-half of the standard deviation for the EOS group. Differences in medication dosages were also computed using a two-way ANOVA allowing for heteroskedasticity. All the tests were two-tailed; significance was defined as $p < .05$.

RESULTS

The EOS patients were younger than the NCs and LOS patients (Table 1). The NCs included a larger proportion of women than the LOS group, and the LOS group had a higher percentage of women than EOS subjects. No significant differences were found between EOS and LOS groups in levels of education, but both had less education than the NC subjects. The NCs were more likely than the participants with schizophrenia to be to be currently or ever married, LOS patients being intermediate between EOS and NC groups. The diagnosis remained stable in most patients followed longitudinally.

There were no significant differences between EOS and LOS groups in terms of the proportion of patients with paranoid subtype. The EOS group had a higher mean daily dose of antipsychotics than the LOS group. The AIMS total was worse for the two schizophrenia groups relative to the NCs, with no differences between EOS and LOS patients. Both the schizophrenia groups had worse psychopathology scores than the NCs, with the LOS group having less severe positive symptoms and general psychopathology relative to EOS group. There were no significant differences between the EOS and LOS groups in severity of negative, deficit (PDS total), or depressive symptoms. There was also no significant difference between the two patient groups in prevalence of Deficit Syndrome (using the published cut-score of PDS total ≥ -2 defined “Deficit Syndrome Status”).

On cognitive testing, both the schizophrenia groups had significantly worse scores than NC subjects. There were no significant EOS-LOS differences on tests of crystallized verbal knowledge (Information, Vocabulary, and Similarities) or auditory working memory (Arithmetic). The LOS group was less impaired than the EOS group on tests of processing speed (Digit Symbol), abstraction/cognitive flexibility (WCST), and verbal memory (CVLT). The LOS patients also had a better performance on one of the two tests of perceptual-organization abilities (Block Design), but not on the other (Picture Arrangement). With regard to everyday functioning and health-related quality of life, the NCs performed better than either of the patient groups, and the LOS group performed better than the EOS group on all three measures (UPSA, SSPA, and QWB).

With the sole exception of severity of positive symptoms (PANSS positive syndrome score), all of the above mentioned EOS-LOS differences remained significant after adjusting for severity of negative or deficit symptoms. On co-varying for duration of illness, two additional differences became non-significant – i.e., differences in cognitive flexibility (WCST), and verbal memory (CVLT); however, the other differences remained significant, including severity of general psychopathology (PANSS general psychopathology score), processing speed (Digit Symbol), perceptual organization (Block Design), everyday functioning (UPSA, SSPA), and health-related quality of life (QWB).

DISCUSSION

We compared the demographic, clinical, neurocognitive, and everyday functioning characteristics of a large sample of middle-aged and older persons with LOS relative to EOS patients and NC subjects. Consistent with our *a priori* hypotheses: (1) LOS and EOS groups had greater levels of psychopathology, cognitive impairment, and functional disability than NC subjects. (2) Relative to the EOS group, LOS patients had a higher proportion of women, less severe positive symptoms and general psychopathology, less severe impairment in abstraction/cognitive flexibility, verbal memory as well as in everyday functioning, and were on lower doses of antipsychotics. (3) With the sole exception of severity of positive symptoms, all of the EOS-LOS differences remained significant after adjusting for age- and gender-corrected scores on severity of negative or deficit symptoms. On co-varying for duration of illness, two additional differences became non-significant – i.e., differences in cognitive flexibility, and verbal memory; however, the other differences remained significant, including severity of general psychopathology, processing speed, everyday functioning, health-related quality of life, and one of the two measures of perceptual organization.

One hypothesis that was not supported was that of a lower severity of negative and deficit symptoms (or prevalence of Deficit Syndrome) in LOS. An unexpected finding was that LOS patients also had faster performance on a measure of processing speed and one (Block Design) but not the other (Picture Arrangement) test of perceptual-organization skills. The difference in processing speed was particularly surprising as the LOS group was, on average, six years older than the EOS group, and processing speed tends to decline steadily with normal aging (86). The better performance of the LOS patients on Block Design could, however, be viewed as suggesting better perceptual organization, and thus consistent with better score on the executive function test (WCST), although the lack of significant differences on the Picture Arrangement task, which also tends to be sensitive to perceptual organization, suggests a need to further examine this potential relationship with additional measures in follow-up research. The differences in results with the two tests of perceptual organization may reflect on the relative psychometric strengths of each of these measures (87).

Although we had a large sample size and employed standardized instruments, our study also had several limitations. While our analyses were directed as tests of several specific *a priori* hypotheses, doing so involved a large number of comparisons to determine if LOS differed from EOS across clinical symptoms, cognition, and daily function, as well as the analyses controlling for potential confounds such as duration of illness, severity of negative symptoms and deficit syndrome. There is a possibility of type I errors because of multiple comparisons, but the direction of significant differences was generally consistent with the patterns seen in earlier (albeit smaller sample size) studies (reviewed by Howard et al. (2)).

As hypothesized, we found a higher proportion of women among LOS than EOS patients. As a non-epidemiologic sample, the relative population prevalence rates of EOS and LOS among women versus men cannot be definitively determined from the present data. (Unfortunately, the prevalence of LOS can also not be estimated from the Epidemiologic Catchment Area Study data because the diagnostic criteria that were employed in that study excluded a diagnosis of schizophrenia in anyone whose symptoms first manifested at age 40 or later (88,89)). Nonetheless, the observed higher frequency of women in the LOS relative to EOS group is consistent with a large body of published empirical data dating back a century. For instance, in his 1911 textbook Eugen Bleuler (10), commenting on age-of-onset data published in a 1907 (German-language) paper by Ryssia Wolfsohn, wrote that:

> "It seems noteworthy though, that in Wolfsohn's material the curve of male patients drops in fairly regular fashion from a maximum in the fifth quinquennium; while that of the female patients shows a small elevation between the ages of 40 and 45 years; this rise becomes even more striking in the two following pentads in which we find more female cases than male. It may very well be due to the influence of climacterium which leaves a much stronger imprint on the female psyche than on the male who after all does not need to resign yet at this particular age period" (pp. 341-242).

Although Bleuler's psychogenic explanation is open to debate, his comments are remarkable in anticipating contemporary theories on the role of menopause (albeit referencing its biological rather than psychosocial aspects) as an explanation for the higher proportion of women among persons with LOS. The so-called "estrogen hypothesis" is that estrogen may mimic some properties of antipsychotic compounds and thus delay symptom onset in women predisposed to schizophrenia until the post-menopausal years (90,91). Definitive evidence for the estrogen hypothesis is lacking, however. Indeed, it would not help explain the occurrence of LOS among men, and it would seem to suggest a stronger antipsychotic effect of estrogen than has been empirically demonstrated. In regard to the latter, clinical trials examining the effectiveness of estrogen replacement as an adjuvant antipsychotic treatment in post-menopausal women with schizophrenia have yielded mixed results, with some reporting positive benefits (92) but others showing no clear added value (93). One potential direction for future research on LOS would be to compare large samples of men and women with LOS to see whether the women have a more severe form of schizophrenia (as the male LOS patients presumably had no or minimal hormonal protection masking the manifestation of schizophrenia).

Another potential interpretive limitation of the present study is that most of the patient participants were clinically stable, receiving maintenance outpatient psychiatric care, and thus had relatively low severity of symptoms. Thus, our results may not generalize to institutionalized patients. However, among other (positive as well as deleterious) effects of the move toward deinstitutionalization of those with chronic mental illnesses that occurred in the last five decades (94), one clear result has been that most of the older persons with schizophrenia currently reside in the community, not in institutions (95). The sample was collected over a period of two decades, and the sample sizes for individual measures varied, but we conducted annual inter-rater reliability training to ensure a sustained high level of reliability. The analyses in this report focus on cross-sectional comparison of baseline data, but the diagnosis of schizophrenia remained stable in most of the patients who were followed longitudinally in our Research Center. It is also important to emphasize that our observed distinctions between EOS and LOS were based primarily on clinical assessments rather than on validated biomarkers (which are not established yet).

The higher antipsychotic dosages among EOS relative to LOS patients are consistent with findings from case registry (96) and open label studies suggesting that LOS patients may be effectively managed on lower doses (reviewed in Howard et al (2)). However, as ours was not an intervention trial, medication type and doses varied across subjects as determined by their individual treating clinicians. It is, therefore, conceivable that the LOS-EOS differences in antipsychotic dosages could be partially due to a tendency to continue prescribing higher doses to EOS patients (who received their first antipsychotic prescription in an era when average dose recommendations were higher for first-break psychosis). Thus the currently higher doses among EOS patients could potentially reflect the residual/ anchoring effects (clinicians being hesitant to change medication doses for clinically stable patients.) It is also possible that dosing differences could be partially attributable to secondary factors, such as episodes of hostility or aggression being less prevalent among

LOS compared to EOS patients. These possibilities warrant controlled clinical trials to determine the lowest effective doses in each group.

One conclusion that can be drawn from the present data is that most of the EOS-LOS differences cannot be explained by differential presence of Deficit Syndrome in the EOS group. The absence of significant differences in the mean PDS scores or the proportion of patients categorized as having Deficit Syndrome when PDS scores were treated categorically, suggests that differential presence of Deficit Syndrome was not responsible for EOS-LOS differences in other dimensions. The latter conclusion was further supported by the lack of a change in the pattern of findings when comparisons were adjusted for differences in PDS scores.

A comparison of the neurocognitive deficits between EOS and LOS groups revealed results that were, on the one hand, consistent with the notion that schizophrenia is best characterized by a general pattern of multiple cognitive deficits of mild-to-moderate severity (56). On the other hand, our finding of less severe impairment among LOS patients in abstraction/cognitive flexibility and verbal memory is also noteworthy. As abstraction/cognitive flexibility tends to be mediated by the executive functions associated with the frontal and frontal-subcortical systems (97,98), and performance on verbal memory measures can be affected by executive functions as well as by the memory consolidation systems in the medial temporal lobe (99), these findings are consistent with the long-standing focus on the prefrontal and temporal lobe regions, as well as their subcortical circuits as viable candidates for neurobiologic systems relevant to the manifestation of schizophrenia (100,101)

One of the challenges in studying the effects of age of onset is that it tends to be confounded with duration of illness, cumulative treatment, and number of prior periods of acute psychotic exacerbations - i.e., relative to similarly aged patients with EOS, those with LOS have had less time for exposure to the potential neurotoxic (and cognitively and socially “toxic”) effects of chronic schizophrenia and its treatment. There is, however, strong basis in the literature to argue against attributing all the EOS versus LOS differences to duration/chronicity or related effects. For instance, cognition tends to be relatively stable throughout the post-adult lifespan in schizophrenia, and there is no significant influence of duration of illness on the severity or pattern of neurocognitive functioning, even when examined within specific ability areas (54,55,63,64). Thus, our finding that EOS-LOS differences in WCST and CVLT no longer reached significance after adjusting for duration of illness could reflect a Type II error. Given that the comparisons were made in terms of residual scores that were, in part, age adjusted, and that with current age, age of illness onset, and duration of illness can be directly triangulated, it may be expected that several of the LOS-EOS differences would fail to reach significance when adjusting for duration of illness.

As expected, both EOS and LOS groups were less likely to have been married and had worse everyday functioning than NCs, but LOS patients were more likely to have been currently or previously married, had better scores on measures of daily functioning and health-related quality of life than EOS patients, and were on lower dosages of antipsychotics, suggesting better prognosis for LOS than for EOS. As was noted earlier, later age of onset has been associated with better course and outcome in several medical disorders such as diabetes mellitus (31), Huntington disease (32), and Alzheimer disease (33).

One may question whether age of onset of schizophrenia is a continuous variable or a categorical one that may be used to define LOS (52). As the current debate regarding appropriate classification and terminology of schizophrenia and associated conditions

continues (102), consistent with the recommendations that emerged from the International Consensus Statement (2), the present results support denoting LOS as a subtype in the future ICD-11 and DSM-V. On the other hand, the value of categorical subtypes over dimensional ratings is itself an issue of ongoing discussion. We believe that these two views are not mutually exclusive. In social life, we use specific age cut-offs to determine the minimum ages for driving, voting, being elected to a public office, or for retirement, although there are no magic changes that take place on those predetermined birthdays.

Given some of the observed group differences, including those in everyday functioning, the EOS-LOS distinction may have clinical value. Obtaining information on age of onset of illness is a part of any well conducted psychiatric interview, and thus does not require administration of additional rating scales or other complex research instruments as is required for some of the other suggested subtypes of schizophrenia. The EOS-LOS differentiation may also have relevance in elucidating the neurobiological basis of schizophrenia. Most researchers accept neurodevelopmental theories of schizophrenia (103). Prior reports demonstrate similarity among EOS and LOS patients in terms of family history of schizophrenia in first-degree relatives, as well as minor physical anomalies and early childhood maladjustment, which may indicate prenatal or early postnatal damage (2,104). Thus, the concept of LOS does not negate neurodevelopmental theories, but rather suggests that neurobiologic changes occurring in mid- or later-life may also be important in the phenotypic manifestation of schizophrenia in some individuals (105). Those changes could represent a diminution of earlier protective factors and/or an accumulation of risk factors. The eventual validity of any subtypes of schizophrenia will be determined by reliable biomarkers, but at present, there are no established biomarkers to define any of the established or suggested subtypes.

In sum, our results suggest that LOS and EOS show sufficient overlap to warrant consideration as a single disorder (commensurate with the heterogeneity between and within other schizophrenia subtypes), yet there are important differences with regard to gender, symptom severity, executive impairment (relevant to adaptive functioning and cognitive rehabilitation efforts (58,106,107)), health-related quality of life, everyday functioning, and other prognostic indicators that should warrant specification of LOS as a subtype. Doing so has heuristic value in facilitating further study of LOS; the insights gained from such research may also open new avenues for prevention and treatment that could be applied to persons with EOS and even to those at high risk for schizophrenia.

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Table 1

Comparison of Normal Subjects and Persons with Early- Versus Late-Onset Schizophrenia on Demographic, Clinical, Cognitive, and Functional Measures

	N (NC, EOS, LOS)	Normal Comparison Subjects (NC)	Early- Onset Schizophrenia (EOS)	Late-Onset Schizophrenia (LOS)	*F*, *t*, or X^2	df	p	Pairwise Significant Differences
Demographic characteristics								
Age (years)	(359,744,110)	59.8 (14.5)	51.0 (8.3)	57.6 (8.7)	75.5	2,278	<.001	EOS<LOS=NC
Education (years)	(359, 738,110)	13.9 (2.3)	12.2 (2.4)	12.5 (3.1)	64.6	2,277	<.001	LOS=EOS<NC
Gender (% women)	(359, 744,110)	63%	34%	47%	84.0	2	<.001	NC>LOS>EOS
Ethnic background % Caucasian	(359, 744,110)	70%	64%	66%	3.6	2	.163	
Marital status	(358, 736,110)				208.6	4	<.001	EOS≠LOS EOS≠NC LOS≠NC
Divorced/Widowed/Separated		41%	41%	55%				
Married/Cohabitating		43%	10%	16%				
Single		16%	49%	29%				
Clinical characteristics								
Age of illness onset (years)	(n/a, 744,110)	n/a	22.9 (7.4)	48.1 (7.3)		n/a[a]	n/a[a]	n/a[a]
% Paranoid subtype	(n/a, 541,71)	n/a	33%	36%	0.2	1	.615	
Duration of illness (years)	(n/a, 744,110)	n/a	28.1(10.2)	9.4 (7.6)		n/a[a]	/n/a[a]	n/a[a]
Daily dose of antipsychotic medication (mg chlorpromazine equivalent)	(n/a, 485, 65)	n/a	477 (888)	135 (96)	−8.1	541.2	0.002	
Abnormal Involuntary Movement Scale score	(168, 637,101)	1.8 (1.9)	4 (3.7)	4.4 (4.6)	150.6	2,234	<.001	NC<EOS=LOS
Positive and Negative Syndrome Scale								
Positive Syndrome score	(356, 740,110)	8.3 (1.9)	15.5 (6.1)	14.0 (6)	367.9	2,278	<.001	NC<LOS<EOS
Negative Syndrome score	(355, 741,109)	8.2 (1.7)	15.0 (5.6)	14.0 (5.3)	545.0	2,272	<.001	NC<LOS=EOS
General Psychopathology score	(354, 740,109)	19.3 (3.1)	30.2 (8.5)	27.9 (6.6)	482.1	2,291	<.001	NC<LOS<EOS
Proxy for Deficit Syndrome (PDS) score[b]	(743,110)	n/a	n/a	−6.5 (3.5)	72.7	2,292	<.001	EOS=LOS
% with Deficit Syndrome (PDS ≥ −2 defining Deficit Syndrome status) [b,59]	(743, 110)	n/a	n/a	6.4%	1.18	1	.278	EOS=LOS

	N (NC, EOS, LOS)	Normal Comparison Subjects (NC)	Early- Onset Schizophrenia (EOS)	Late-Onset Schizophrenia (LOS)	*F*, *t*, or X^2	df	p	Pairwise Significant Differences
Hamilton Rating Scale for Depression score	(354, 688,110)	3.6 (3.7)	10.4 (6.4)	9.7 (6.1)	218.7	2,295	<.001	NC<EOS=LOS
Cognitive performance								
WAIS-R or WAIS-III (Reference group Scaled Scores)								
Information	(152, 270,54)	10.4 (2.7)	9.4 (3.2)	9.2 (3.2)	49.9	2,139	<.001	EOS=LOS<NC
Vocabulary	(165, 299,56)	11.1 (2.8)	8.4 (3.2)	8.9 (3.1)	42.4	2,149	<.001	EOS=LOS<NC
Similarities	(145, 284,56)	10.1 (2.7)	7.9 (3.3)	8 (3.3)	71.2	2,146	<.001	EOS=LOS<NC
Picture Arrangement	(147, 270,53)	8 (2.8)	6.8 (2.9)	6.6 (3.2)	31.9	2,135	<.001	EOS=LOS<NC
Block Design	(146, 263,55)	7.9 (2.5)	6.5 (2.4)	7 (3.1)	56.4	2,135	<.001	EOS<LOS<NC
Arithmetic	(148, 276,57)	9.1 (2.8)	7.1 (2.8)	7.6 (3.5)	52.3	2,141	<.001	EOS=LOS<NC
Digit Symbol	(150, 431,70)	7 (2.4)	4.7 (1.8)	5.3 (2.4)	140.3	2,155	<.001	EOS<LOS<NC
WCST Perseverative Responses (T-score)	(155, 362,62)	49.8 (12.9)	39.3 (13.2)	45 (15.7)	31.4	2,151	<.001	EOS<LOS<NC
California Verbal Learning Test (CVLT)	(157, 197,42)	10.1 (3.3)	9.2 (3.6)	10.7 (3.4)	3.9	2,117	.023	EOS<LOS=NC
Functional capacity and Quality of life								
UCSD Performance-based Skills Assessment score	(31, 417,53)	92.6 (5.8)	67.6 (20.6)	72 (18.8)	112.4	2,71	<.001	EOS<LOS<NC
Social Skills Performance Assessment score	(110, 462,56)	37.3 (4)	26.4 (8)	28.4 (8.2)	416.8	2,133	<.001	EOS<LOS<NC
Quality of Well-Being scale (Adjusted score)	(158, 494,77)	0.7 (0.1)	0.5 (0.1)	0.6 (0.1)	99.2	2,179	<.001	EOS<LOS<NC

Note: Higher scores on Abnormal Involuntary Movement Scale, Positive and Negative Syndrome Scale, and Hamilton Rating Scale for Depression represent worse symptoms. Higher scores on the Proxy for Deficit Syndrome, as well as all the cognitive, functional capacity, and Quality of Well-Being measures represent better status.

[a] Means (and SDs) for age of onset and duration of illness are provided for descriptive purposes only. The significance of these differences was not statistically tested because the null hypotheses (no difference in the EOS versus LOS populations) are, by definition, known to be false.

[b] Deficit syndrome measures were not applied to normal comparison subjects.

Abbreviations:
EOS = Early-Onset Schizophrenia
LOS = Late-Onset Schizophrenia
n/a = not applicable
NC = Normal Comparison subject
UCSD = University of California, San Diego

WAIS-R = Wechsler Adult Intelligence Scale – Revised
WAIS-III = Wechsler Adult Intelligence Scale – Third Edition

Table 2

Schizophrenia Group Differences after Adjusting for Group Differences in Duration of Illness, Severity of Negative Symptoms, or Proxy for Deficit Syndrome Scores.

	Severity of Negative Symptoms			Proxy for Deficit Syndrome			Duration of Illness		
Dependant Variables	**F**	**df**	**p-value**	**F**	**df**	**p-value**	**F**	**df**	**p-value**
PANSS positive syndrome score	2.51	1, 827	0.114	3.75	1, 834	0.053	1.56	1, 839	0.212
PANSS general psychopathology	5.48	1, 827	0.019	9.00	1, 834	0.003	4.99	1, 838	0.026
WCST Perseverative responses	4.06	1, 410	0.044	5.13	1, 411	0.024	0.96	1, 414	0.328
CVLT Memory score	6.94	1, 224	0.009	6.70	1, 229	0.010	0.04	1, 228	0.844
Digit Symbol	12.44	1, 486	0.001	17.85	1, 487	0.001	8.31	1, 490	0.004
Block Design	4.95	1, 304	0.027	5.92	1, 307	0.016	5.24	1, 307	0.023
UPSA	10.40	1, 459	0.001	10.96	1, 456	0.001	8.43	1, 460	0.004
SSPA	10.19	1, 505	0.002	10.58	1, 505	0.001	8.88	1, 508	0.003
Adjusted QWB	6.82	1, 552	0.009	10.14	1, 558	0.002	4.64	1, 560	0.032

Note: Due to significant age and gender differences among the groups (Table 1), each of the outcome variables was replaced with a standardized age- and gender-corrected version. (Please see the section on Statistical Analysis for details.)

Abbreviations:
CVLT – California Verbal Learning Test
PANSS – Positive And Negative Syndrome Scale
QWB – Quality of Well-Being scale
WCST – Wisconsin Card Sorting Test