What Is the Evidence for Changes in Cognition and Functioning Over the Lifespan in Patients With Schizophrenia?

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Cognitive deficits in schizophrenia are important predictors of impairment in most functional domains and are a critical therapeutic target. These deficits appear at or before the onset of illness, are stable across time in most patients, and can be improved by cognitive remediation treatments. Recent evidence, however, suggests that cognitive function does not necessarily follow a pattern of age-related decline. Several studies evaluated this pattern of decline in schizophrenia patients compared to both natural aging and degenerative conditions such as Alzheimer's disease. Age-related differences were not comparable to either normal aging or Alzheimer's disease. Older patients with an extensive history of illness and protracted institutionalization have shown a greater progressive decline. These deficits were also observed in older patients who were no longer institutionalized, with these patients demonstrating decline in functional capacity across time compared to healthy controls and patients with no lengthy institutional stay. There were 2 clear conclusions from this body of data. First, there appear to be 2 separate periods of deterioration in schizophrenia patients. These patients appear to decline the most at 2 key time points; the first occurs some time prior to the first psychotic episode and the second begins at approximately 65 years of age. The second important conclusion is that these 2 important periods of time may be the time point at which an aggressive intervention may have the greatest impact.

(J Clin Psychiatry 2014;75[suppl 2]:34–38)

Schizophrenia is a mental disorder characterized by a breakdown of thought processes and impaired emotional responses. Common symptoms include delusions, auditory hallucinations, disorganized speech, and a lack of emotional response. It is a highly debilitating and chronic illness that leads to disruptions in functioning. Schizophrenia patients demonstrate declines in many aspects of everyday functioning, including impairments in social, cognitive, and real-world activities that are often detectable prior to the first episode of illness.

In recent years, interest in the relationship between cognitive and functional impairments in patients with schizophrenia has grown.[1] Cognitive deficits are important predictors of impairment in most functional domains and are viewed as a critical therapeutic target.[2] These deficits typically appear at or before the onset of illness,[3] are stable across time in most patients,[4] appear to worsen predominantly in the oldest patients,[5] and can be improved by cognitive remediation treatments.[6]

The idea that cognitive function has a normal course of age-related decline in all adults and that this decline is generally mirrored in schizophrenia patients is generally supported by the empirical data. However, recent evidence suggests that this may not be true in 100% of cases. The present review will examine the evidence supporting the idea that there is a lifetime course of schizophrenia and discuss data from several unique cohorts.

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doi:10.4088/JCP.13065su1.08

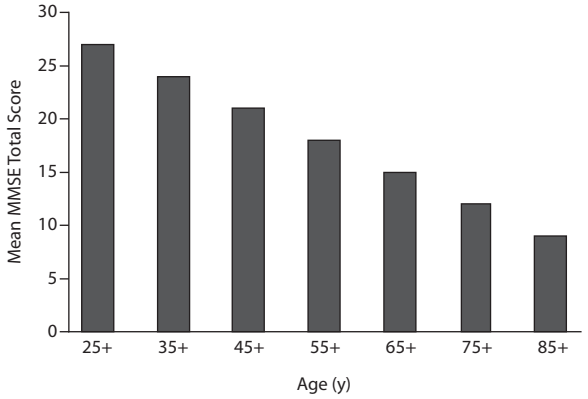
EVIDENCE OF CHANGES IN COGNITION AND FUNCTIONING ACROSS THE LIFESPAN

The course of cognitive function in older schizophrenia patients was evaluated in a large-scale longitudinal study at Pilgrim Psychiatric Center. The assessment strategy focused on adults with schizophrenia at least 55 years old and was initiated approximately 25 years ago. A unique characteristic in this sample was that the patients had no antipsychotic medication available at the time of their schizophrenia incidence, resulting in untreated psychosis due to a lack of therapeutic options. Schizophrenia patients exhibited evidence of decline in cognitive function, with a 3-point-per-decade difference across the sample in Mini-Mental State Examination (MMSE) functioning (Figure 1).[7]

Interpreting the meaning of these cross sectional differences is critical. If they reflect true longitudinal change unique to schizophrenia, they should be distinctive from healthy aging and from degenerative conditions such as Alzheimer's disease (AD). Healthy people do not exhibit detectable changes in MMSE scores until very late in life.[8] Further, MMSE scores in patients with AD decrease by approximately 3 points per year.[8]

This differing rate of decline from both healthy aging and degenerative conditions led to a follow-up evaluation of these patients. The cross-sectional differences in cognitive functions in patients with schizophrenia and those with AD was the focus of the first of these studies. When the 2 patient groups were compared, results indicated that schizophrenia and AD patients were different on most cognitive indices.[9] Schizophrenia patients were significantly worse on praxic functioning and verbal skill domains, while AD patients were predictably worse at delayed recall and recognition; rate of episodic memory learning was not significantly different.

Figure 1. Mini-Mental State Examination (MMSE) Scores in Poor-Outcome Patients[a]



[a]Based on data from Davidson et al.[7]

The key finding from these data was that schizophrenia and AD patients do not appear to have the same brain impairment on the basis of cognitive performance. This conclusion was based primarily on the minimal amount of overlap of cognitive impairment, with the profile in AD patients implicating a cortical dementia profile with prominent deficits in medial temporal lobe functioning.

In another study[10] from this program of research, the cognitive, clinical, and functional characteristics of lifelong chronic schizophrenia were examined in 3 samples of patients. One included a sample of long-term institutionalized patients, another included a group of long-term institutionalized patients previously discharged to nursing home care, and the third was an acutely admitted sample with no more than 6 weeks of institutionalization. Results indicated that the severity of psychotic symptoms was essentially identical in the 3 groups. Acutely admitted patients had dramatically higher cognitive and adaptive function than those who were chronically institutionalized for numerous years. The cognitive performance between the 3 groups spanned approximately 5 standard deviations, with the acutely admitted patients performing about 2 standard deviations below normative standards. These results suggested that both groups of long-term patients were displaying gross levels of impairment. However, the correlation between daily function, rated by clinical staff while patients were hospitalized, and cognitive performance was essentially identical across all 3 groups. In essence, there were no differences in the relationship between cognitive ability and everyday functioning across the 3 samples, regardless of whether the patient had spent 10 days in acute treatment or 50 years in a state psychiatric facility.

DO THESE DATA IMPLICATE COGNITIVE DECLINE IN SCHIZOPHRENIA PATIENTS?

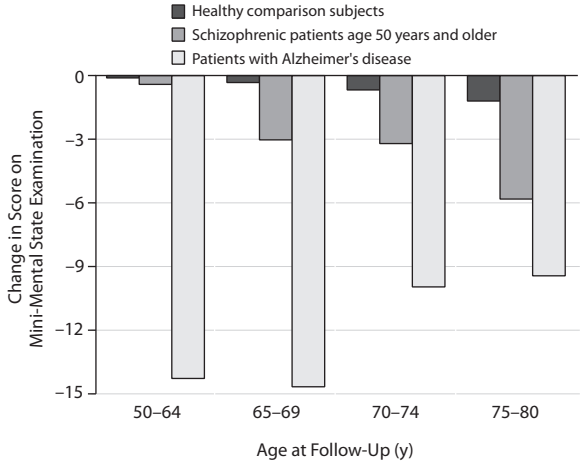
The predominant question originated from these data centers on whether the cognitive decline in schizophrenia patients comes across the lifespan or centers on a selected sample of older patients. There has been debate as to whether these cognitive deficits are neurodevelopmental in origin and thus static over time. In a study[11] aimed to address this question, chronically hospitalized patients over the age of 65 were followed longitudinally (N = 500) for 5 years, in which the key outcome was meeting a dichotomous criterion for worsening. In this analysis, worsening was defined as a patient going from a clinical dementia rating (CDR) score of 1 or less to a CDR score of 2 or more. The CDR is frequently used in dementia research and is useful in compiling a composite measure of cognition and functioning. Results indicated a 48% risk of worsening across the 60-month assessment period.[11] Although this difference was significant, the amount of change in each individual patient over the 5-year period was not dramatic, equivalent to a decline of approximately 3 MMSE points.

These results were contrasted by the comments from a review article that appeared concurrently.[12] The author of that article concluded that the studies to date indicated no evidence for cognitive decline. However, these conclusions can be questioned given that the studies examined included only samples of young schizophrenia patients (none older than 60) being examined longitudinally for very brief periods. Further, the sample size for all of the studies in this review totaled fewer patients than the sample evaluated by Harvey and Davidson.[11] As a result, the entire collection of previous studies included none of the patients studied in the Pilgrim Psychiatric Center sample.

A longitudinal study[13] from that research effort examined healthy individuals, people with AD, and people with schizophrenia to determine whether there was evidence of an age-associated risk of worsening. This study evaluated 118 mild to moderate AD patients at study entry (aged 50–80 years), 132 healthy adults (again, 50–80 years), and 107 schizophrenia patients (aged 25–80 years), all followed for 6 years. The results indicated that healthy individuals lost an average of a single MMSE point over the 6-year follow-up period, reflecting minimal cognitive change. AD patients lost 10 to 14 MMSE points over the follow-up period, regardless of their age at study entry. In the schizophrenia patients, there was a distinct pattern of worsening that was associated with age. For the schizophrenia patients 50 to 64 years old, there was a minimal risk of worsening that was approximately 0.5 MMSE point per year (Figure 2). For older patients with schizophrenia, the risk of worsening was substantially greater, with an apparent inflection point at age 65.

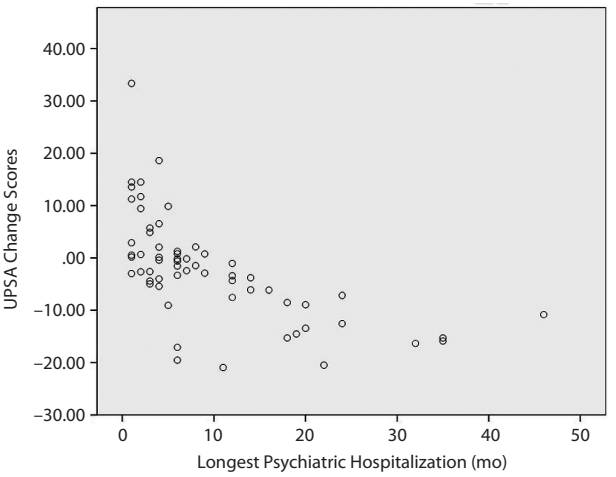
There are several key features of this study.[13] First, these patients were institutionalized for an extended period of time and thus were not at risk for many of the common comorbidities of community-dwelling patients, such as abusing substances (eg, alcohol, illicit drugs) due to lack of availability. Further, adherence to daily medication was at or near 100% because patients were not given an option. The absence of these 2 factors was not trivial, particularly given that they are considered important risk factors for deterioration in ambulatory schizophrenia patients.[14] Additionally, the controlled environment in this study enabled adequate handling of other medical factors such as high blood pressure and cholesterol. The average age at death in this sample was 78.5.[15] Community standards for

Figure 2. Effect of Age on 6-Year Mini-Mental State Examination Change Scores for Healthy Subjects, Patients With Schizophrenia, and Patients With Alzheimer's Disease[a]



[a]Reprinted with permission from Friedman et al.[13]

Figure 3. Course of UPSA Scores Over the Follow-Up Period[a]



[a]Reprinted with permission from Harvey et al.[17]
Abbreviation: UPSA = University of California, San Diego (UCSD) Performance-Based Skills Assessment.

life expectancies of people born at the time of this sample (approximately during the years 1912 to 1925) were actually lower than this (ranging from 52 for men born in 1912 to 58 for men born in 1925, with similar ranges for women: 56–61 [http://www.demog.berkeley.edu/~andrew/1918/figure2.html]). Further, recent research has suggested that schizophrenia patients have a life expectancy that is reduced by approximately 20 years compared to the general population.[16] These findings combine to suggest that long-stay institutional treatment is not a uniformly negative influence on life expectancy.

There are also several important caveats with regard to these conclusions. Given that institutionalized patients are in the minority,[13] these data should be considered as an extreme case. Decades-long periods of psychosis without treatment are no longer a feature of the illness.

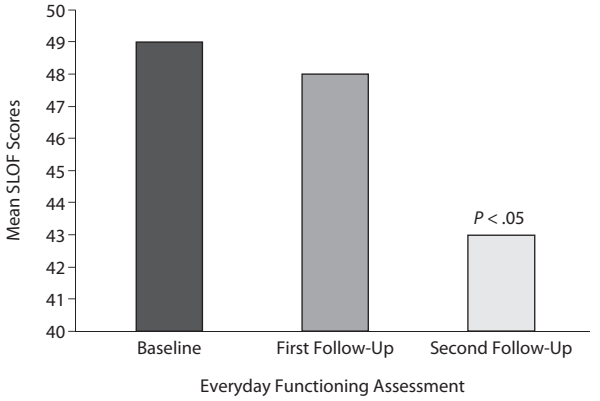
In an attempt to control for the institutionalization confound from the previous study,[13] cognitive and functional decline was examined in ambulatory schizophrenia patients with varied lengths of longest inpatient stays.[17] These institutionalizations lasted from less than 4 weeks up to 36 years and included patients who ranged from acute admission to an extended hospital stay. Every patient recruited into the study[17] was followed for up to 40 months and assessed on up to 2 occasions after baseline. During these assessment periods, data were gathered on functional capacity; the University of California, San Diego (UCSD) Performance-Based Skills Assessment (UPSA); and the Social Skills Performance Assessment (SSPA). Additionally, everyday function was assessed with the Specific Levels of Functioning (SLOF) measure, a rating scale aimed at social, vocational, and residential function.[18]

This analysis is unique for several reasons, including: (1) there has never been a short-term longitudinal study of older patients that was oriented toward decline in everyday functioning; (2) the sample of patients included a subset with a history of extensive institutional stays in the past; (3) the design allowed for the examination of the longitudinal course of influence of previously identified cross-sectional predictors of impairments in everyday functioning in the 3 functional domains of social, community activities, and vocational functioning[19,20]; and (4) the previously identified longitudinal predictors of decline in cognition and function in long-stay inpatients (length of institutional stay, education) were used to predict the longitudinal course of functional skills in patients living in the community.

A mixed-model repeated measures analysis[17] was used to examine changes in functional capacity and cognition and identify potential predictors of change. The ability to perform everyday living skills, or functional capacity, was worse in patients with an extended institutional stay.[17] Conversely, patients with no previous long-term hospitalization demonstrated improvements in functional capacity that were very likely attributable to practice effects. Conclusions from these data indicated a potential institutionalization cutoff point of approximately 6 months that delineated those that declined versus those who either did not decline or improved (Figure 3).[17] Patients clustering around this time point demonstrated no evidence of worsening in performance-based assessments of functioning, despite the fact that most were over the age of 65 years.

Since the Harvey et al 2011 publication,[17] these analyses were expanded to include measures of real-world outcomes.[21] There were several findings of potential interest in this study. First, older schizophrenia patients showed modest worsening in everyday functioning as a group, with these changes being predicted by several variables measured in the previous analyses. Importantly, the previous finding that history of longer institutional stay predicted worsening in performance-based measures was expanded by demonstrating that institutionalization history predicted worsening of real-world function. The results also showed

Figure 4. Specific Levels of Functioning (SLOF) Everyday Functioning Scores Over 3 Assessments[a]



[a]Reprinted with permission from Reichenberg et al.[21]

that worsening in performance on social skills and functional capacity predicted worsening of everyday function in 2 of the 3 everyday functional domains that were measured. Further, these data also suggested that length of institutionalization influenced deficits in real-world function because of the link to deterioration in functional skills. A decline in negative symptoms was also associated with a decline in everyday activities, while the previous cross-sectional influence of depression on everyday functioning was not confirmed in the longitudinal study.

Results indicated that everyday functioning (SLOF) experienced a decline over time (Figure 4).[21] Overall, these data suggested that as scores on the UPSA and SSPA scales deteriorated, there was a corresponding deterioration in everyday functioning.

One of the clear implications of these results was that direct intervention on cognition and functional capacity should be strongly considered. These cognitive remediation interventions have been shown to improve cognition and functioning[22] and to be effective even in some of the most intractable patients.[23] Additionally, these data suggested that reducing the risk factors for cortical deterioration may represent a complementary approach. Finally, these interventions may reduce the subtle progressive cognitive changes seen in some schizophrenic patients.

CONCLUSIONS

The overall picture from these studies is 2-fold. First, it is very clear that there are 2 separate periods of time when everyday functioning in schizophrenia patients appears to deteriorate. Patients with schizophrenia seem to deteriorate the most around the first psychotic episode and at around 65 years of age, irrespective of the age at onset. The second key point is that these are the 2 periods of time when an aggressive intervention may be the best option. Older patients with an extensive history of illness and protracted institutionalization have shown a greater progressive decline.[24,25] These declines have also been observed among patients who are no longer institutionalized, with these patients demonstrating decline in functional capacity across time when compared to healthy controls and patients with no lengthy institutional stay.[17]

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Potential conflicts of interest: **Dr Harvey** received a fee for service from Otsuka America Pharmaceutical, Inc., and Lundbeck for participation in the meeting and preparation of this manuscript and, during the past year, has received consulting fees from Abbvie, Boehringer-Ingleheim, En Vivo, Forest, Genentech, Otsuka America Pharmaceutical, Inc., Sunovion, and Takeda.
Acknowledgments: This article is derived from a roundtable meeting titled "Understanding the lifetime course of schizophrenia: a longitudinal perspective on neurobiology to promote better outcomes and recovery," which was held October 15, 2013. Editorial assistance in developing the manuscript was provided by Healthcare Global Village.
Funding/support: The meeting, manuscript preparation, and dissemination of the supplement were sponsored by Otsuka America Pharmaceutical, Inc., and Lundbeck.

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