Psychiatr Q (2012) 83:127–144
DOI 10.1007/s11126-011-9189-8

ORIGINAL PAPER

Is There Evidence for Late Cognitive Decline in Chronic Schizophrenia?

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Published online: 24 August 2011

Abstract Schizophrenia (SZP) has been historically referred to as "dementia praecox" because of the recognition that its onset is associated with deficits in memory, attention and visuospatial orientation. We wondered whether there is evidence for additional cognitive decline late in the course of chronic SZP. This review examined the evidence (1) for cognitive decline late in the course of chronic SZP, (2) for how often the late cognitive decline occurs, and (3) whether the cognitive decline in late-life SZP is related to pathophysiology of SZP versus the superimposition of another type of dementia. A PUBMED search was performed combining the MESH terms schizophrenia and dementia, cognitive decline, cognitive impairment and cognitive deficits. A manual search of article bibliographies was also performed. We included longitudinal clinical studies employing standard tests of cognition. Cross-sectional studies and those that did not test cognition through standard cognitive tests were excluded. The initial search produced 3898 studies. Employing selection criteria yielded twenty-three studies. Our data extraction tool included the number of patients in the study, whether a control group was present, the age of patients at baseline and follow-up, the study setting (inpatients versus outpatients), the cognitive tests employed, study duration, and results. Only three longitudinal studies tested for

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dementia using Diagnostic and statistical manual of mental disorder (DSM) or International classification of disease (ICD) criteria and compared them to controls: two studies demonstrated an increase in the prevalence of dementia and one did not. Twenty longitudinal studies tested for one or more cognitive domains without employing standard criteria for dementia: twelve studies demonstrated a heterogeneous pattern of cognitive decline and eight did not. Studies generally did not control for known risk factors for cognitive impairment such as education, vascular risk factors, apolipoprotein (ApoE) genotype and family history. The evidence for late cognitive decline in SZP is mixed, but, slightly more studies suggest that it occurs. If it occurs, it is unclear whether it is related to SZP or other risks for cognitive impairment. Hence, prospective, longitudinal, controlled studies are needed to confirm that there is progressive cognitive decline in chronic SZP which occurs independent of other risk factors for cognitive impairment.

Keywords Schizophrenia · Dementia · Cognitive decline · Cognitive impairment · Cognitive deficits

Introduction

Schizophrenia (SZP) is a psychotic disorder which affects 1% of the general population [1]. The characteristic psychotic symptoms usually begin between the ages of 16 and 30 years [1]. There is no gender predilection. The disorder is associated with loss of activities of daily living, social disability, stigma and increased societal costs [2].

SZP has been historically regarded as 'dementia praecox' because cognitive impairment is a common feature of SZP. Cognitive changes occur early in the course of the disease and may persist even after the psychosis abates [3]. Moreover, there is evidence that they may occur before the onset of clinically diagnosed SZP, i.e. pre-morbidly [3]. The cognitive and behavioral changes in SZP are often severe enough to meet standard diagnostic criteria of dementia [4–9].

Another clinical observation is that some patients with SZP appear to experience additional cognitive decline later in course of the illness. When looked at carefully in studies, there is, in fact, evidence that cognitive decline occurs steadily throughout the course of SZP, as might occur in a progressive, neurodegenerative disorder [10, 11]. On the other hand, some studies suggest that the cognitive changes present at the onset of SZP remain static [10] as would be observed when a pathophysiologic process progresses for a period of time, and then arrests. Thus, it is unclear whether patients with SZP show static cognitive dysfunction versus progressive or late cognitive decline.

On the other hand, there are a number of reasons why SZP patient could develop additional cognitive impairment, including dementia, later in the course of the illness. The presence of premorbid cognitive dysfunction and low education levels in most schizophrenics may increase vulnerability to dementia [12, 13]: there may be less "cognitive reserve". Normal aging in the setting of decreased reserve could then lead to a greater risk for dementia in these patients [13]. Chronic SZP patients may also be at an increased risk for cardiovascular disease because of the metabolic syndrome related to a sedentary lifestyle, poor diet, smoking and chronic antipsychotic medication use [14, 15]. Strokes are also more common in SZP patients versus the general population [16], thus, increasing the risk for vascular dementia (VaD). Head injury has been associated with SZP and is also a strong risk factor for dementia [17]. Apolipoprotein E4 genotype increases the risk for AD and many studies suggest an association between Apo E4 and SZP [18–20]. There have

also been reports of high alcohol/substance abuse disorders in SZP patients, which may contribute to the development of dementia [21]. Thus, there are many potential reasons why patients with SZP may have progressive cognitive decline during the course of the disease.

The purpose of this review is to examine the evidence (1) for cognitive decline late in the course of chronic SZP, (2) for how often the late cognitive decline occurs, and (3) whether the cognitive decline in late-life SZP is related to the pathophysiology of SZP versus the superimposition of another type of dementia. Defining a clear association between SZP and dementia would have important implications in terms of understanding the *pathophysiology* underlying SZP, which remains unclear [22]. For example, it could support a progressive neurodegenerative hypothesis versus a static one. It would also have implications for the *management* of SZP. For example, it would suggest that patients with SZP should be screened more regularly for cognitive change and would have important implications for caregiver planning. It would also suggest that their risk factors for cognitive decline should be addressed, wherever possible, throughout the course of SZP to minimize additional cognitive decline. This review should also aid in the design of future studies investigating cognitive decline during the course of SZP.

Methods

We conducted a PUBMED search using the MeSH terms 'schizophrenia' and 'dementia', 'cognitive decline', 'cognitive impairment' and 'cognitive deficits'. The initial search resulted in 3898 articles published between 1960 and 2009 (Fig. 1). Abstracts of all the articles were reviewed by one of the authors (JNS). Articles that did not focus on cognitive impairment in SZP were excluded. This resulted in 324 studies.

The full-texts of these articles were reviewed by JNS. Studies were included if they had a longitudinal design, studied cognitive decline, and defined cognitive decline either by using Diagnostic and statistical manual of mental disorders (DSM) or International classification of disease (ICD) criteria for dementia or through formal cognitive screening tools and/or formal neuropsychological tests (NPTs).

Studies were excluded if a cross-sectional design was adopted ($n = 26$). They were also excluded if the patients were younger than 45 years at the end of the study as this age group would be less likely to have developed dementia ($n = 10$). Studies examining only the neuropathology, neuroradiology or neurobiology of dementia in SZP were excluded since they did not study cognitive decline ($n = 138$). Studies focusing on single cognitive domains were excluded since they did not test enough areas of cognition to form a basis for deciding about whether there was overall cognitive decline ($n = 65$). Case-reports were excluded ($n = 32$) and non-English studies ($n = 29$) were excluded.

References of all the selected studies were reviewed to identify additional articles that did not appear in the initial search. The manual search did not yield any studies which fit the selection criteria. The selected studies were independently reviewed by two authors (JNS, SUQ).

Results

Overall 23 studies met the selection criteria, of which three studies employed DSM/ICD criteria of dementia, whereas 20 studies employed brief cognitive screening tools or NPTs.

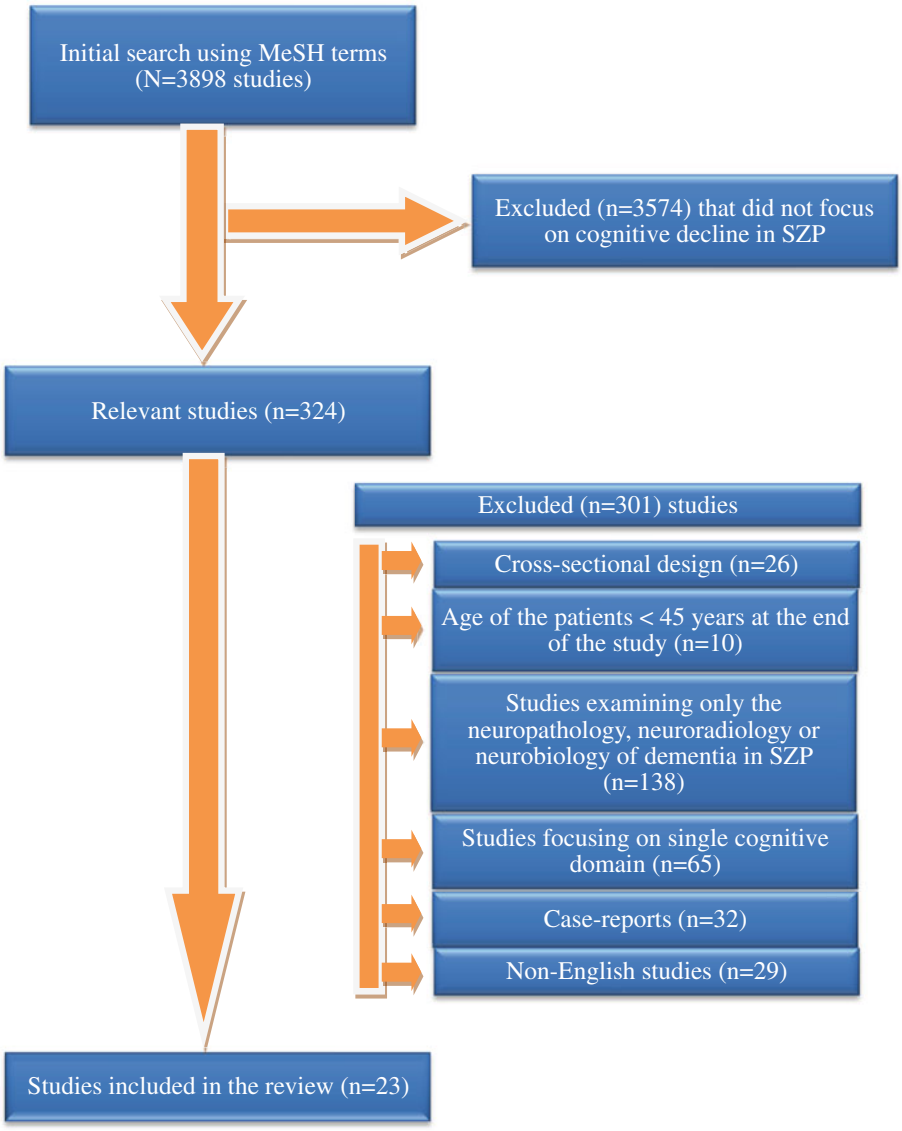

Fig. 1 Literature review process and outcome

The three studies that used DSM/ICD criteria for dementia were performed on patients with late-onset schizophrenia (LOS). Of the 20 studies that used brief cognitive screening tools/NPTs, 17 studies were performed on patients with early-onset SZP (EOS), one study involved LOS patients, and two studies involved patients with both EOS and LOS (Fig. 2).

We defined studies as *positive* if they showed a decline in cognition over the follow-up period. Studies were defined as *negative* if they did not demonstrate a significant decline in cognition over the follow-up period.

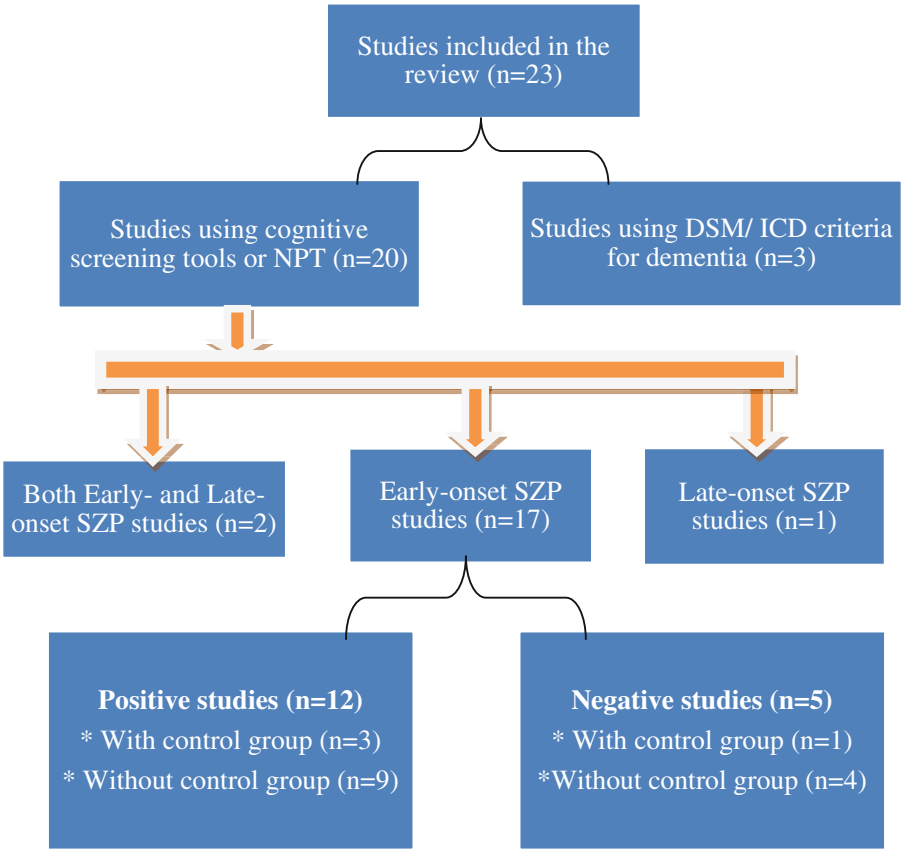

Fig. 2 Classification of the 23 studies included in the review

Studies Employing DSM/ICD Criteria for Dementia Diagnosis ($n = 3$, Table 1)

Only three studies used DSM or the ICD criteria to define dementia [7–9]. All three studies were performed on LOS patients. These studies are briefly described below and summarized in Table 1.

Kørner et al. [7] used the Danish national registry to identify four patient cohorts: late-onset SZP, very late-onset SZP and two control groups (age-matched individuals with osteoarthritis). Diagnoses were based on the ICD9 classification. Patients were followed for 3–4.6 years to ascertain the incidence of dementia. Using Poisson regression models, the relative risks (RRs) of developing dementia in the late and very-late SZP groups versus osteoarthritis patients were 3.47 (95% CI: 2.19–5.50) and 3.15 (95% CI: 1.93–5.14) respectively. Versus the general population, the RRs were 2.36 (95% CI: 1.54–3.62) and 2.21 (95% CI: 1.39–3.50), respectively. Dementia not otherwise specified (NOS) was the most common subtype of dementia identified followed by Alzheimer disease (AD) and vascular dementia (VaD).

Brodaty et al. [8] followed 27 LOS and 34 normal controls for 5 years. Of the 19 patients that completed the five year follow-up, 9 (47%) had developed dementia defined

Table 1 Longitudinal studies of patients with LOS using DSM or ICD definitions for dementia and SZP ($n = 3$)

Author, year	LOS cut-off (years)	*n*	Control	SZP & dementia diagnosis	Duration of F/U (years)	Dementia prevalence at end of F/U (SZP)	Dementia prevalence at end of F/U (Control)
Korner, 2000 [7]	LOS: >40 VLOS: >60	1206, 409	OA, NC	ICD 10	3–4.6	1.7% (LOS) 4.4% (VLOS)	OA: 1.4% OA: 2.15%
Brodaty, 2003 [8]	>50	27	NC	DSM	5	47%	0%
Rabins, 2003 [9]	>44	28	MDD	DSM	10	50%	50%

DSM diagnostic and statistical manual of mental disorder, *ICD* international classification of disease, *SZP* schizophrenia, *LOS* late-onset schizophrenia, *VLOS* very late-onset schizophrenia, *F/U* follow up, *OA* osteoarthritis, *NC* normal controls, *MDD* major depressive disorder

by the DSM-IV criteria. The subtypes were AD ($n = 5$), VaD ($n = 1$), and unknown ($n = 3$). None of the controls developed dementia. Patients who developed dementia were older at baseline, had a lower socio-economic status, had a longer duration of SZP and had worse baseline scores on the Instrumental Activities of Daily Living (IADL) scale, the Activities of Daily Living (ADL) scale and the MMSE. The study suggests that late-onset SZP might be a prelude to dementia within 5 years.

Rabins et al. [9] followed 29 LOS patients for >1 year and compared them to 48 major depressive disorder patients and 47 AD patients with psychosis. The likelihood of developing dementia in the MDD and SZP groups did not differ at 120 months: both groups had an incidence of approximately 50%. The authors suggested that SZP may not be a specific precursor of dementia- any structural brain disease may increase the likelihood of dementia in the elderly.

Studies That Employed Brief Cognitive Screening Tools or Neuropsychological Tests ($n = 20$)

20 studies were identified that used brief or full cognitive tests to examine cognitive function over time in patients with SZP. Seventeen were performed on patients with EOS, one on patients with LOS and two employed both groups.

Studies in Patients With EOS (n = 17, Tables 2 & 3)

Most ($n = 17$) of the longitudinal studies involved EOS patients. Twelve studies were positive and five studies were negative for cognitive decline. These studies are described below based on the presence or absence of control group(s) and are summarized in Tables 2 and 3.

Positive Studies With Controls (n = 3, Table 2) Ortakov et al. [23] retrospectively evaluated clinical charts of 26 elderly SZP patients and found a mean increase in the sum of Clinical Dementia Rating scale (CDR) items by 1.0 (range 0.26–2.2) point per decade over the course of 51 years of the illness. This was compared to patients in the CERAD (The Consortium to Establish a Registry for Alzheimer's disease) database [24], which consists of normal elderly individuals. The mean sum of the CDR items increased in the

Table 2 Longitudinal studies employing brief or extensive cognitive batteries in patients with EOS that found significant cognitive decline at follow-up (positive studies, $n = 12$)

No.	Author, year	*n*	Comparison group	Mean age at B/L and/or F/U	IP/OP	Duration of F/U (years)	Cognitive scales used	Key results in SZP	Key results in controls
1	Ortakov, 1999 [23]	26	400 NC from CERAD 1996 database	81 at F/U	IP	51	CDR	Increase in sum of CDR items by 1.0 (range 0.26–2.2) points per decade of illness	Increase from 0 (in sixth decade) to 1.0 (in 10th decade)
2	Friedman, 2001 [25]	107	136 NC 118 AD	20–80 at B/L (50 < 65 years) (57 > 65 years)	IP	6	CDR, MMSE	CDR: Risk of cognitive decline 5.7% (<40 years), 0% (40–65 years), 37.5% (65–70 years), 75% (70–75 years), 100% (75–80 years)	CDR: Risk of cognitive decline in AD 85–95% for all >65 years; NC-no decline
3	Morrison, 2006 [28]	43	12 different psychiatric disorders	61 at F/U	36 OP 7 IP	33	RSPM, MVHS	RSPM-decline; MVHS-stable	RSPM & MVHS stable
4	Ciompi, 1980 [4]	289	None	33–47 at B/L	OP	37	Interviews (not defined)	17% intermediate deterioration, 8% severe	
5	Waddington, 1996 [29]	41	None	54 at B/L	IP	10	10-question mental test	Decline in males aged >55 years	
6	Harvey, 1999 [30]	326 160 (CDR < 2) 166 (CDR > 2)	None	73 at B/L	IP	2.5	CDR	28 (27.6%) of CDR < 2 declined to CDR ≥ 2	
7	Harvey, 1999 [31]	57	None	78 at B/L	IP	2.6	MMSE	Decline by 4 points MMSE	
8	Friedman, 2002 [32]	124	None	72 at B/L	IP	4	CERAD	Decline on composite score	

Table 2 continued

No.	Author, year	*n*	Comparison group	Mean age at B/L and/or F/U	IP/OP	Duration of F/U (years)	Cognitive scales used	Key results in SZP	Key results in controls
9	Harvey, 2003 [33]	424 280 low functioning (CDR $\geq$ 2 at B/L) 144 high functioning (CDR $\leq$ 1 at B/L)	None	Low functioning: 79 at B/L High functioning: 72 at B/L	IP	6	ADAS-L	Both groups showed equal magnitude of decline on composite measure	
10	Meagher, 2004 [34]	129	None	69 at B/L	IP	2.9	MMSE, EXIT	MMSE declined by 6%; EXIT increased by 25%. MMSE dropped by 1pt over 3 years	
11	Chemerinski, 2006 [35]	334 a: 111 deficit b: 40 non-deficit-delusional c: 56 non-deficit-disorganized)	None	65 at B/L	IP	6	MMSE ADAS-L Cog	MMSE Decline in a, b; ADAS-L Cog decline in a, b, c	
12	White, 2006 [36]	175 Poor outcome SZP (B/L MMSE 12-14)	None	72–75 at B/L	IP?	5.5	MMSE, ADAS-L Cog (composite)	Cognitive decline in all patients	

SZP schizophrenia, *EOS* early onset schizophrenia, *MMSE* mini mental state examination, *CDR* clinical dementia rating scale, *ADAS-L* Alzheimer's disease assessment scale late version, *EXIT* executive interview, *CERAD* consortium to establish a registry for Alzheimer's disease, *RSPM* Raven's standard progressive matrices, *MVHS* Mill hill vocabulary scale, *B/L* baseline, *F/U* follow up, *IP* inpatient, *OP* outpatient, *NC* normal control, *AD* Alzheimer's disease

Table 3 Longitudinal studies employing brief or extensive cognitive batteries in patients with EOS that did not find significant cognitive decline at follow-up (negative studies, $n = 5$)

No.	Author, year	*n*	Comparison group	Mean age at B/L (yrs)	IP/OP	Duration of F/U (years)	Cognitive scales used	Key results in SZP	Key results in controls
1	Savla, 2006 [37]	143	66 NC (62 years)	53	OP	1.75	MDRS	17% declined on global and subscale measures	17% declined
2	Harvey, 1995 [38]	224	None	76	IP	1–2	MMSE	Stable. No significant decline. MMSE 13.4 at 1 year	
3	Harvey, 1996 [39]	174	None	75	IP + OP	1	MMSE, CERAD	Stable. No significant decline in any test	
4	Harvey, 1996 [40]	302 a. 84 MMSE $\geq$ 24 b. 60 MMSE:18–23 c. 58 MMSE:10–17 d. 100 MMSE $<$ 10	None	69	IP	1	MMSE, CERAD	Stable. No significant decline on any subscale	
5	McGurk, 2000 [41]	168	None	74	IP	1.25	CERAD	Slight decline in praxis and verbal fluency	

SZP schizophrenia, *LOS* late onset schizophrenia, *MMSE* mini mental states examination, *MDRS* Mattis dementia rating scale, *CERAD* consortium to establish a registry for Alzheimer's disease, *NC* normal control, *B/L* baseline, *F/U* follow up, *IP* inpatient, *OP* outpatient

CERAD cohort from 0 in the sixth decade to 1.0 in the tenth decade. The authors concluded that there is a faster rate of cognitive decline in SZP patients versus the normal elderly population.

Friedman et al. [25] assessed cognitive functioning in 26 SZP patients (aged 20–80 years) over a period of 6 years using the MMSE and the Clinical Dementia Rating (CDR) scale. Worsening of cognition was defined as progression of CDR score from less than 2 at baseline to 2 or higher at follow up. The risk of cognitive decline increased with age, especially in those aged above 65 years, as follows: 5.7% (<40 years), 0% (40–65 years), 37.5% (65–70 years), 75% (70–75 years) and 100% (75–80 years). The comparison group, composed of patients with AD, showed a steady risk of 85–90% in all those aged above 65 years, while the age-matched normal control group did not show any decline.

Morrison et al. [28] utilized Raven's Standard Progressive Matrices [26] to assess general and verbal intelligence and the Mill Hill Vocabulary Scale [27] to assess non-verbal intelligence in SZP patients over a period of 33 years. As compared to the control group composed of other psychiatric disorders, the SZP patients showed a significant decline in verbal intelligence over time.

Positive Studies Without Controls (n = 9) (Table 2) Ciompi et al. [4] reported data from 289 EOS patients that were followed for about 37 years. Patients were evaluated for the presence of 'psycho-organic aging syndrome' based on their cognitive functioning assessed through a structured interview. Twenty-three percent of patients had no change in cognitive function, 35% showed minor impairment, 17% had intermediate symptoms (definite thought and memory disturbances), and 8% fit the criteria for 'amnesic psycho-syndrome' with total spatial and temporal disorientation. There was no control group, but the authors reported that the prevalence in the general population >65 years old from other studies was 6–15% for intermediate 'organic psychosyndromes' (versus 17% for SZP) and 3–6% for severe syndrome (versus 8% in SZP). Hence, the authors concluded that organic dementias appeared to be more frequent in chronic schizophrenics than in an age-matched general population.

Waddington et al. [29] assessed the performance of middle-aged patients with SZP on a brief 10-question mental test over a five to ten year follow-up period and reported a modest deterioration in cognitive performance.

Two studies conducted by Harvey et al. used dementia screening tools such as the CDR and MMSE to assess cognitive decline over a period of approximately 2.5 years [30, 31]. The first study defined worsening of cognitive function as an increase of CDR score from less than 2 to at least 2 or higher. Over a period of 30 months, 27.6% patients showed worsening. Old age, lower levels of education and the presence of positive symptoms at baseline were identified as risk factors for cognitive decline [30]. The second study found a moderate level of decline in elderly institutionalized SZP patients where average MMSE score dropped from 10 at baseline to 6 at the end of 2.6 years [31].

Friedman et al. [32] studied cognitive decline in SZP patients in the context of medical co-morbidities. They examined elderly institutionalized patients using the CERAD battery [24]. Over a period of 4 years, they observed a significant decline on the composite CERAD score (-0.06 to -0.36, $P < 0.001$), which was associated with functional decline in these patients, independent of medical co-morbidities.

In another study by Harvey et al. [33], patients were divided into high functioning (CDR $\leq$ 1) and low functioning (CDR $\geq$ 2) groups at baseline and were followed up for 6 years. At the end of the follow-up, both groups showed equal magnitudes of decline on the Alzheimer's disease assessment scale late version (ADAS-L) cognitive subscale

composite measure. However, there was a higher functional decline in the low functioning group. A higher risk for cognitive decline was observed in females, patients with earlier age of onset for SZP, and those with more severe negative symptoms at baseline.

Meagher et al. [34] studied SZP patients using the MMSE and Executive Interview (EXIT). They found that MMSE declined by 6% (16.2–15.2, $P < 0.05$) over 2.9 years and EXIT scores increased by 25% (17–21.2, $P < 0.001$), which indicates worsening of executive functions. The drop in MMSE of 1 point over 3 years was more prominent in males, older patients and patients on anti-cholinergic medications at the follow-up assessment.

Chemerinski et al. [35] studied cognitive and functional decline over 6 years in elderly SZP patients over the age of 65 years. Patients were categorized as having one of the three-syndromes at baseline: "deficit", "non-deficit-delusional" and "non-deficit-disorganized". The first two groups showed a significant decline in MMSE scores ($P < 0.01$), and all three groups showed significant declines in the ADAS-L cognitive and self-care scores ($P < 0.0001$).

White et al. [36] assessed MMSE and ADAS-L Cog scores longitudinally over a period of 5.5 years in elderly poor-outcome SZP patients (baseline MMSE: 12–14) treated with first-generation or second-generation antipsychotic medications. They found that cognitive functions declined over time for both the groups and this decline was not modified by treatment with any of the anti-psychotic medications.

Negative Study With Controls ($n = 1$, Table 3) Nayak Savla et al. [37] compared the cognitive performance of SZP patients to normal controls on the MDRS over a period of 15 months using hierarchical linear modeling. Both groups showed a stable cognitive performance over time.

Negative Studies Without Controls ($n = 4$, Table 3) Harvey et al. [38–40] conducted three short studies (1995–1996) over a period of 1–2 years on elderly SZP patients (age above 65 years). No significant decline in cognition was observed using MMSE and its subscale scores in the first study [38] and a CERAD neuropsychological battery and composite MMSE scores in the second study [39]. In the third study, patients were divided into four groups on the basis of their baseline MMSE scores. At the end of the follow-up period, there was no evidence of cognitive decline, regardless of baseline MMSE scores [40].

McGurk et al. [41] conducted a study on elderly SZP patients using the CERAD battery. Although a slight but significant decline in praxis and verbal fluency over a 15 month period was observed, the overall pattern of cognitive function was stable.

Study on Patients With LOS ($n = 1$, Table 4)

There is only one longitudinal study by Laks et al. [42] which employed brief cognitive screening tools to check for progressive cognitive decline in patients with LOS. They used the MMSE and cognitive and self-contained part of the Cambridge examination for mental disorders of the elderly (CAMCOG) to follow Brazilian LOS patients and found no significant decline over 1 year. The study is listed in Table 4.

Studies on Patients With Both EOS and LOS ($n = 2$, Table 4)

In two studies, both EOS and LOS patients were tested on performance on NPTs to ascertain cognitive decline late in the course of SZP. These results of these studies are described below and summarized in Table 4.

Table 4 Longitudinal studies employing brief or extensive cognitive batteries in patients with LOS, or both EOS & LOS

No.	Author, year	EOS/LOS	*n*	Comparison group	Mean age at B/L (years)	IP/OP	Duration of follow-up (years)	Cognitive scales used	Key results in SZP	Key results in controls
1	Heaton, 2001 [43]	EOS + LOS	142	NC	55	OP	5	NPTs	Minimal cognitive decline	Minimal cognitive decline
2	Palmer, 2003 [44]	EOS + LOS	69 EOS 37 LOS	AD, AD with psychosis, NC	EOS: 60 LOS: 63 AD: 72 NC: 63	OP	1.4	MMSE, MDRS	Minimal cognitive decline in SZP groups	Significant cognitive decline in AD
3	Laks, 2006 [42]	LOS	13	None	66	OP	1	MMSE, CAMCOG	Stable cognitive performance	

SZP schizophrenia, *EOS* early onset schizophrenia, *LOS* late onset schizophrenia, *NPT* neuropsychological test, *MMSE* mini mental state examination, *MDRS* Mattis dementia rating scale, *CAMCOG* Cambridge examination for mental disorders of the elderly, *NC* normal control, *AD* Alzheimer's disease, *B/L* baseline, *F/U* follow up, *IP* inpatient, *OP* outpatient

Heaton et al. [43] compared SZP patients to normal controls in a longitudinal study of cognitive function. They used a comprehensive NPT battery and found that NP impairment remained stable over a period of 5 years. This occurred regardless of current age, age of onset of illness, baseline level of NP impairment, improvement and worsening of clinical symptoms and occurrence of tardive dyskinesia.

Palmer et al. [44] tested for 1- and 2-year changes on the MMSE and Mattis Dementia Rating scale (MDRS) in early-onset SZP spectrum disorders, late-onset SZP spectrum disorders, AD patients with psychosis, AD patients with cognitive impairment and normal controls. The two SZP groups and the normal control group had stable cognitive test results, while the AD patients showed decline in cognition.

Discussion

We reviewed 23 longitudinal studies of patients with chronic SZP that tested for the development of dementia or cognitive decline late in the course of the disease. Only 3 studies utilized a formal definition for dementia as defined by DSM and ICD criteria: two studies were positive and one was negative for development of dementia. 20 studies used brief or extensive cognitive batteries to test for changes in cognition longitudinally. In this category, there were 17 EOS studies, and 12 were positive and 5 were negative. There was one LOS study that was negative. Two studies involved both EOS and LOS patients and both were negative. Overall, 14 studies were positive and 9 were negative, with a positive to negative ratio of 1.5:1. However, if we limit the studies to only those with control groups, the positive to negative ratio is 1.2:1.

Evidence for Late Cognitive Decline in Schizophrenia

Development of Dementia

Three studies used DSM or ICD criteria to diagnose dementia. All three had control groups. Two concluded that dementia was more common in LOS after 3–5 years. However the study with the longest follow-up (10 years) found no difference in the prevalence of dementia versus controls (50 vs. 50%). Moreover, the prevalence of dementia between the three studies differed dramatically at 1.7, 47, and 50%. Another important consideration is that none of the studies controlled for known risk factor factors for dementia, such as vascular disease, head trauma, family history, ApoE genotype, education, etc. Considering these limitations, it is not possible to conclude whether the prevalence of dementia late in the course of SZP is above the expected rate or not.

Progressive Cognitive Deterioration as Assessed Through Cognitive Screening Tools or Neuropsychological Tests

Twenty studies used brief or extensive cognitive batteries to test for changes in cognition longitudinally. Of the EOS studies ($n = 17$), 12 were positive, of which only 3 had control groups. Five were negative, and four had control groups. The only LOS study (uncontrolled) as well the two studies testing both EOS and LOS patients (controlled) were negative.

Several differences are noted between the positive and negative studies. The negative studies had shorter follow-up periods (mean = 1.4, range = 1–1.75 years versus mean = 11.8 years, range = 2.5–51 years for the positive studies). The ages of the patients at the end of the follow-up periods were lower in the negative studies (ranges of 49–76 years vs. 64–83 years for the positive studies). Additionally, there is heterogeneity in the study population characteristics: half of the negative studies were conducted using outpatient populations, whereas the majority of the positive studies were conducted using inpatient populations. Thus, differences in study design may contribute to differences in results. Considering the differences in results and differences in study design, one might conclude that there is modest evidence for progressive decline of cognitive functioning in SZP, but the findings need to be examined further through well-designed prospective studies.

Early Onset Versus Late Onset Schizophrenia

There were 17 studies on patients with EOS with a positive to negative ratio of 2:1. In the LOS category, there were four studies and the positive to negative ratio is 1:1. Two studies involved both population groups and were negative for significant cognitive decline. The EOS studies had longer periods of follow up (range: 1–51 years) than the LOS studies (range: 1–10 years), which would appear to make them more likely to capture cognitive deterioration. However, if we limited the analysis to studies with control groups, the ratio in the EOS studies was 1:1 ($n = 3$ to $n = 3$) and in LOS was 3:2. Thus, it appears that the evidence for a difference in the risk of late cognitive impairment between EOS and LOS is inconclusive.

Is Late Cognitive Decline in SZP Related to the Pathophysiology of SZP or due to Superimposition of Another Dementia?

This question could be answered by looking at the individual cognitive domains affected at follow up and ascertaining whether these domains were the same as those affected at baseline, which would suggest that dementia was related to SZP. The majority of studies reviewed here only utilized brief or global cognitive assessment tools, such as the MMSE, CDR, DRS or CERAD. Only composite scores of the screening tools were used to detect a change in cognition. Only one study (Heaton et al. [43]) employed an extensive neuropsychological battery to identify changes in multiple cognitive domains. Because we were unable to ascertain the domains that changed, this review was unable to establish whether it is likely that late cognitive decline in SZP is due to progression of SZP versus the superimposition of another type of dementia.

The three studies that examined the development of dementia also did not indicate a particular subtype of dementia that developed late in some patients with SZP.

Limitations to the Reviewed Studies

A number of factors complicate the interpretation of the studies presented here. A major limitation is the heterogeneity in the study designs. There are differences in the definitions of dementia, SZP and cut-offs for LOS. There are also differences in the duration of follow-up; the study size; the use of control groups (more than half did not have control groups, $n = 14$) and the types of control groups (normal, AD, MDD, osteoarthritis, etc.);

whether there were controls for variables known to be associated with the development of dementia (e.g., education, ApoE status, head trauma); whether and how patients were screened before full NP testing, the NPTs employed; and, whether patients were on medications at the time of testing and the duration of their use. All these make it difficult to directly compare findings across studies.

Most of the selected studies had small sample sizes and short durations of follow-up. Additionally, most studies were performed on chronically hospitalized patients with possible long-term antipsychotic medication usage and institutionalization. Antipsychotic medications are known to impact cognitive performance [45–49]. Psychotic symptoms might also confound the evaluation of cognition, though it has been suggested that only the negative symptoms of SZP affect NPT performance, and that effect is minor [50–52].

Conclusions

We reviewed evidence for progressive cognitive deterioration and the development of dementia in chronic SZP patients. There is a relatively even split in terms of positive and negative controlled studies, and hence it remains unclear whether dementia or cognitive change occurs at an increased rate later in the course of SZP versus controls. Moreover, there is a great deal of heterogeneity in the way these studies have been conducted, which limits the ability to compare studies and draw conclusions.

The potential association between SZP and dementia is very interesting, but it thus appears to require a well-designed, longitudinal study for substantiation. We would suggest that such a study should use validated criteria for the diagnosis of dementia and schizophrenia. It should include modern diagnostic and imaging techniques to improve diagnostic accuracy and to prevent misdiagnosis. It should control for other known risk factors for dementia, including education, age, vascular risk factors (hypertension, diabetes, etc.), ApoE4 genotype, and a history of significant head trauma. It should control for medication use at the time of cognitive testing. It should have control groups that are matched in terms of the aforementioned variables. Finally, the age at onset of schizophrenia might be more homogeneous and there should be an emphasis on determining the subtypes of dementia present.

Well-designed studies are likely to reveal the true prevalence of dementia in chronic schizophrenia, and ascertain whether that dementia is caused by SZP or is due to the coincidental presence of another form of dementia.

Conflict of interest None.

References

1. Schizophrenia-U.S. Department of Health and Human Services, National Institutes of Health National Institute of Mental Health NIH Publication No. 09-3517 Revised 2009
2. Barbato A: Schizophrenia and Public health. Nations for Mental Health. WHO/MSA/NAM/97.6, 1998
3. Asarnow RF: Neurocognitive impairments in schizophrenia: A piece of the epigenetic puzzle. European Child & Adolescent Psychiatry 8(Suppl 1):I5–8, 1999
4. Ciompi L: Catamnestic long-term study on the course of life and aging of schizophrenics. Schizophrenia Bulletin 6(4):606–618, 1980

5. de Vries PJ, Honer WG, Kemp PM et al.: Dementia as a complication of schizophrenia. Journal of Neurology, Neurosurgery & Psychiatry 70(5):588–596, 2001
6. Banaschewski T, Schulz E, Martin M, Remschmidt H: Cognitive functions and psychopathological symptoms in early-onset schizophrenia. European Child & Adolescent Psychiatry 9(1):11–20, 2000
7. Kørner A, Lopez AG, Lauritzen L et al.: Late and very-late first-contact schizophrenia and the risk of dementia—a nationwide register based study. International Journal of Geriatric Psychiatry 24:61–67, 2009
8. Brodaty H, Sachdev P, Koschera A, et al.: Long-term outcome of late-onset schizophrenia: 5-year follow-up study. The British Journal of Psychiatry 183:213–219, 2003
9. Rabins PV, Lavrisha M: Long-term follow-up and phenomenologic differences distinguish among late-onset schizophrenia, late-life depression, and progressive dementia. American Journal of Geriatric Psychiatry 11:6, 2003.
10. Goldberg TE, Hyde TM, Kleinman JE, et al.: Course of schizophrenia: neuropsychological evidence for a static encephalopathy. Schizophrenia Bulletin 19:797–804, 1993
11. Lieberman JA: Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. Biological Psychiatry 46(6):729–739, 1999
12. Farmer ME, Kittner SJ, Rae DS, et al.: Education and change in cognitive function. The Epidemiologic Catchment Area Study. Annals of Epidemiology 5:1–7, 1995
13. Corral M, Rodríguez M, Amenedo E et al. Cognitive reserve, age, and neuropsychological performance in healthy participants. Developmental Neuropsychology 29(3):479–491, 2006
14. Cohn T, Prud'homme D, Streiner D et al.: Characterizing coronary heart disease risk in chronic schizophrenia: High prevalence of the metabolic syndrome. Canadian Journal of Psychiatry 49(11):753–660, 2004
15. Stahl SM, Mignon L, Meyer JM: Which comes first: Atypical antipsychotic treatment or cardioembolic risk? Acta Psychiatrica Scandinavica. 119(3):171–179, 2009
16. Lin HC, Hsiao FH, Pfeiffer S, et al.: An increased risk of stroke among young schizophrenia patients. Schizophrenia Research 101(1–3):234–241, 2008
17. Malaspina D, Goetz RR, Friedman JH, et al.: Traumatic brain injury and schizophrenia in members of schizophrenia and bipolar disorder pedigrees. The American Journal of Psychiatry 158:440–446, 2001
18. Dean B, Laws SM, Hone E, et al.: Increased levels of apolipoprotein E in the frontal cortex of subjects with schizophrenia. Biological Psychiatry 54(6):616–622, 2003
19. Schürhoff F, Krebs MO, Szöke A, et al.: Apolipoprotein E in schizophrenia: A French association study and meta-analysis. American Journal of Medical Genetics B: Neuropsychiatric Genetics 119B (1):18–23, 2003
20. Hata T, Kunugi H, Nanko S, et al.: Possible effect of the APOE epsilon 4 allele on the hippocampal volume and asymmetry in schizophrenia. American Journal of Medical Genetics 114(6):641–642, 2002
21. Jeste DV, Gladsjo JA, Lindamer LA, et al.: Medical comorbidities in Schizophrenia. Schizophrenia Bulletin 22(3):413–430, 1996
22. Niizato K, Genda K, Nakamura R, et al.: Cognitive decline in schizophrenics with AD a mini-review of neuropsychological and neuropathological studies. Progress in Neuro-Psychopharmacology & Biological Psychiatry 25:1359–1366, 2001
23. Ortakov V, Mancevski B, Keilp J, et al.: Application of cognitive scales to medical records of schizophrenia inpatients. Schizophrenia Research 35(2):131–140, 1999
24. CERAD: CERAD 1986–1996, Documentation and Data. Archive Rev 1.0, March 1996. Durham, NC, 1996
25. Friedman JI, Harvey PD, Coleman T, et al.: Six-year follow-up study of cognitive and functional status across the lifespan in schizophrenia: A comparison with Alzheimer's disease and normal aging. The American Journal of Psychiatry 158(9):1441–1448, 2001
26. Raven JC: Standard Progressive Matrices. London, Lewis, 1958a
27. Raven JC: The Mill Hill Vocabulary Scale. London, Lewis, 1958b
28. Morrison G, O'Carroll R, McCreadie R: Long-term course of cognitive impairment in schizophrenia. The British Journal of Psychiatry 189:556–557, 2006
29. Waddington JL, Youssef HA: Cognitive dysfunction in chronic schizophrenia followed prospectively over 10 years and its longitudinal relationship to the emergence of tardive dyskinesia. Psychological Medicine 26(4):681–688, 1996
30. Harvey PD, Silverman JM, Mohs RC, et al.: Cognitive decline in late-life schizophrenia: A longitudinal study of geriatric chronically hospitalized patients. Biological Psychiatry 45(1):32–40, 1999
31. Harvey PD, Parrella M, White L, et al.: Convergence of cognitive and adaptive decline in late-life schizophrenia. Schizophrenia Research 35(1):77–84, 1999
32. Friedman JI, Harvey PD, McGurk SR, et al.: Correlates of change in functional status of institutionalized geriatric schizophrenic patients: Focus on medical comorbidity. The American Journal of Psychiatry 159(8):1388–1394, 2002

33. Harvey PD, Bertisch H, Friedman JI, et al.: The course of functional decline in geriatric patients with schizophrenia: Cognitive-functional and clinical symptoms as determinants of change. American Journal of Geriatric Psychiatry 11(6):610–619, 2003
34. Meagher DJ, Quinn JF, Bourke S, et al.: Longitudinal assessment of psychopathological domains over late-stage schizophrenia in relation to duration of initially untreated psychosis: 3-year prospective study in a long-term inpatient population. Psychiatry Research 126(3):217–227, 2004
35. Chemerinski E, Reichenberg A, Kirkpatrick B, et al.: Three dimensions of clinical symptoms in elderly patients with schizophrenia: prediction of six-year cognitive and functional status. Schizophrenia Research 85(1–3):12–19, 2006
36. White L, Friedman JI, Bowie CR, et al.: Long-term outcomes in chronically hospitalized geriatric patients with schizophrenia: Retrospective comparison of first generation and second generation antipsychotics. Schizophrenia Research 88(1–3):127–134, 2006
37. Nayak Savla G, Moore DJ, Roesch SC, et al.: An evaluation of longitudinal neurocognitive performance among middle-aged and older schizophrenia patients: Use of mixed-model analyses. Schizophrenia Research 83(2–3):215–223, 2006
38. Harvey PD, White L, Parrella M, et al.: The longitudinal stability of cognitive impairment in schizophrenia. Mini-mental state scores at one- and two-year follow-ups in geriatric in-patients. The British Journal of Psychiatry 166(5):630–633, 1995
39. Harvey PD, Lombardi J, Leibman M, et al.: Cognitive impairment and negative symptoms in geriatric chronic schizophrenic patients: A follow-up study. Schizophrenia Research 22(3):223–231, 1996
40. Harvey PD, Lombardi J, Leibman M, et al.: Performance of chronic schizophrenia patients on cognitive neuropsychological measures sensitive to dementia. International Journal of Geriatric Psychiatry 11:621–627, 1996
41. McGurk SR, Moriarty PJ, Harvey PD, et al.: The longitudinal relationship of clinical symptoms, cognitive functioning, and adaptive life in geriatric schizophrenia. Schizophrenia Research 42(1):47–55, 2000
42. Laks J, Fontenelle LF, Chalita A, et al.: Absence of dementia in late-onset schizophrenia: A one year follow-up of a Brazilian case series. Arq Neuropsiquiatr 64(4):946–949, 2006
43. Heaton RK, Gladsjo JA, Palmer BW, et al.: Stability and course of neuropsychological deficits in schizophrenia. Archives of General Psychiatry 58(1):24–32, 2001
44. Palmer BW, Bondi MW, Twamley EW, et al.: Are late-onset schizophrenia spectrum disorders neurodegenerative conditions? Annual rates of change on two dementia measures. The Journal of Neuropsychiatry and Clinical Neurosciences 15(1):45–52, 2003
45. Lewis R: Should cognitive deficit be a diagnostic criterion for schizophrenia? Journal of Psychiatry & Neuroscience 29(2):102–113, 2004
46. Waddington JL, Youssef HA, Dolphin C, et al.: Cognitive dysfunction, negative symptoms and tardive dyskinesia in schizophrenia. Archives of General Psychiatry 44(10):907–912, 1987
47. Liddle PF, Crow TJ.: Age disorientation in chronic schizophrenia is associated with global intellectual impairment. The British Journal of Psychiatry 144:193–199, 1984
48. Spohn HE, Strauss ME: Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia. Journal of Abnormal Psychology 98(4):367–380, 1989
49. Goldberg TE, Weinberger DR: Effects of neuroleptic medications on the cognition of patients with schizophrenia: A review of recent studies. Journal of Clinical Psychiatry 57(Suppl 9):62–65, 1996
50. Galderisi S, Davidson M, Kahn RS, et al.: Correlates of cognitive impairment in first episode schizophrenia: The EUFEST study. Schizophrenia Research, 2009
51. Chen EY, Lam LC, Chen RY, et al.: Negative symptoms, neurological signs and neuropsychological impairments in 204 Hong Kong Chinese patients with schizophrenia. The British Journal of Psychiatry 168:227–233, 1996
52. Norman RM, Malla AK, Morrison-Stewart SL, et al.: Neuropsychological correlates of syndromes in schizophrenia. The British Journal of Psychiatry 170:134–139, 1997

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