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What do we really know about late-onset schizophrenia ?

Abstract Actual knowledge on classical late-onset schizophrenia, i.e. the schizophrenic disorders with onset after age 40 years, is reviewed regarding incidence, symptomatology and course. As is shown, sound empirical knowledge is scarce. Reasons for this are, on the one hand, the conceptual and terminological confusion which has occurred internationally regarding this illness group, and, on the other hand, the methodological limitations of the empirical studies conducted on this clinical picture thus far. If we only draw on *classical* late-onset schizophrenia, as originally defined by Bleuler, and primarily on methodologically sound studies, as well as on own studies, we can nevertheless conclude that the term "late-onset schizophrenia" could be omitted. Late-onset schizophrenia does not seem to be a distinct entity, but instead seems to belong to the same illness group as classical schizophrenia with earlier onset. Slight differences in symptomatology and course are probably due to unspecific influences of age. The markedly higher proportion of women among late-onset cases, as well as our finding that symptomatology and course of late-onset women are comparably poor, could possibly be explained by an effect of the female sex hormone oestradiol.

Key words Late-onset schizophrenia · Epidemiology · Symptomatology · Course · Late paraphrenia

Introduction

Since the time schizophrenic diseases – then still called "Dementia praecox" – were first described by Kraepelin (1893), it has been generally accepted that most cases occur before the age of 40 years. On the other hand, the illness – or a similar illness – has also been described to begin at a more advanced age in some cases. Since then there have been many efforts to differentiate these late-onset psychoses from the group of the classical schizophrenias with early onset, i.e. before age 40 years, based on their symptomatology, risk factors and course.

Manfred Bleuler presented the first comprehensive empirical work on these psychoses and coined the term "late-onset schizophrenia". According to his definition these diseases are kinds of schizophrenic psychoses with onset after age 40 years, but mainly before age 60 years. They resembled the classical early-onset schizophrenia in their clinical picture, although he also found certain differences: "in somewhat more than half of late-onset schizophrenics we see a symptom colouring as it has been described as somehow characteristic and especially frequent: paraphrenia-like states on the one hand, depressive-anxious-catatonic on the other hand, and additionally a small group of confused agitations which can be easily mistaken for amentia. In the second, smaller half of the late-onset schizophrenics, symptomatology does not show anything differing from early-onset schizophrenics" (translated from M. Bleuer 1943, p. 283). Many authors after Bleuler have subsequently also found certain differences between late and early-onset schizophrenias as regards symptomatology. Even more equivocally described was from the very beginning another difference between late- and early-onset cases, namely an intriguing excess of women in late-onset schizophrenics.

These characteristics have again and again raised the question of whether late-onset schizophrenia should be regarded as a separate diagnostic entity, aetiologically (at least partially) differing from early-onset schizophrenia. The term "late-onset schizophrenia" has subsequently become widely accepted. In 1987 it was even included in the DSM-III-R.

But what do we really know about this illness (group)? Are there really decisive differences between late- and early-onset schizophrenia patients which would even justify the use of an extra diagnostic label for this illness

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group? Do these late-onset cases not belong instead to the same group of diseases as the classical early-onset schizophrenias? The following is an attempt to answer these questions based on a comprehensive literature review and on own studies.

Literature review

The literature review includes all articles and monographs published during this century in English or German either on late-onset schizophrenia or on similar illness groups before this diagnostic label was coined. Based on computerized literature search (MEDLINE; PSYCLIT) and standard text- and handbooks, including the references found in these articles and books, we could identify 121 articles published up to 1995. All studies were analysed concerning their methodological standards: number and selection of patients, diagnostic criteria, kind of investigation, definition of onset, exclusion criteria, representativity of the sample, restriction to first admitted or first episode patients, etc. Drawing mainly on studies with relatively sound methodology we then tried to summarize the scarce knowledge on incidence, prevalence, gender distribution, symptomatology and course.

Methodological considerations: How sound is our knowledge?

Unfortunately, the validity of the existing findings on late-onset schizophrenia is seriously restricted by two major problems, namely the confusion of terms and concepts which has developed internationally regarding this illness group (Riecher-Rössler et al. 1995), and the methodological shortcomings of the empirical studies conducted thus far.

As to the concept "late-onset schizophrenia", German-language psychiatry has largely adopted that of Bleuler and labels as "late-onset schizophrenia" only those clinical pictures which resemble early-onset schizophrenia but have their onset after age 40 years. They usually occur before age 60 years and do not have an organic basis. Other, mainly Anglo-American, authors use the term late-onset schizophrenia also for the paranoid psychoses of old age with onset after age 60 years. According to British tradition the latter clinical pictures have also been called "late paraphrenia". Thus, internationally there has not been a clear differentiation between late-onset schizophrenia of German tradition and late paraphrenia of British tradition. As a consequence of this many findings on so-called late-onset schizophrenia are in fact based on populations with late paraphrenia or on mixed diagnostic groups and are only of limited validity regarding late-onset schizophrenia itself.

An additional problem concerns age limit. In German psychiatry this has been fixed at age 40 years, in Anglo-American psychiatry partly at age 45 years (in accordance with DSM-III), partly even at age 60 years. The latter age limit mainly resulted from the previously mentioned confusion between late-onset schizophrenia and late paraphrenia. Furthermore, it usually is not said clearly, how "onset" is operationalized. Usually, it is simply equated with "first admission" which, as we now know, on average occurs only approximately 4–5 years after the first signs of the beginning disease (Häfner et al. 1992b, 1993a,b).

As to the methodology of the studies conducted thus far, Table 1 gives an overview of the studies since Kraepelin (1919) and describes their most important methodological aspects and limitations:

1. main problem is that almost all studies (see Table 1) have thus far only been done on selected patient groups, e.g. on patients of a certain hospital for chronically ill, and the results can therefore not be generalized.

2. For the same reason there are no very reliable calculations on prevalence or incidence, which would have to be based on *all* cases in a defined population.

3. In most studies it was not distinguished between first and readmitted patients (see Table 1, e.g. Klages 1961; Angst et al. 1973; Huber et al. 1975; Pearlson et al. 1989; Marneros et al. 1992; Yassa and Suranyi-Cadotte 1993; Jeste et al.1995). This means that the comparison group of early-onset patients had on average a much a longer course of their disease and therefore more signs of chronicity. A comparison with the relatively fresh clinical picture of the late-onset patients is in this case not very valid. Only few studies were restricted to first admissions (Funding 1963; Hinterhuber 1973; Marneros and Deister 1984; Mayer et al. 1993; Häfner et al. 1993a, b).

4. In many studies early-onset patients were not compared empirically, but comparisons were only made on the basis of literature (e.g. Klages 1961; Siegel and Rollberg 1970; Rabins et al. 1984).

5. In the older studies neither standardized diagnostic systems (see Table 1) nor standardized assessment instruments were in use (e.g. Bleuler 1943; Retterstøl 1966). Often the analyses were retrospective only, based on case notes and not on direct investigations (e.g. Rabins et al. 1984; see also Table 1).

Nevertheless, the great advantage of some – mainly European – studies is that very big populations were examined thoroughly and over long periods of time (e.g. on average 17.8 years by Huber et al. 1975, or even 30–40 years by Hinterhuber 1973).

Results of studies: What do we really know?

As to the results of the studies conducted thus far, it has to be stated that, despite the differing methodology, some findings are astonishingly similar. Other results are, in contrast to that, very inconsistent and even contradictory, so that many questions are unanswered.

Results on age-related risk

The proportion of patients with illness onset after age 40 years among those actually examined in most studies lies between 15 and 25% (e.g. Kolle 1931; Bleuler 1943; Fish 1958; Astrup 1962; Retterstøl 1966; Hinterhuber 1973; Huber et al. 1979). Results differing from this might partly be due to the fact that life expectancy and therefore age composition has changed over time. They are partly due to differing methodologies. Thus for example Kraepelin (1919) and Schulz (1933) found lower proportions of 5.8 and 5.3%, respectively, as they excluded the subgroup of "paraphrenia" which is supposed to have a comparably late disease onset. On the other hand, for example, Angst et al. (1973) with 35% found a very high proportion of late-onset cases, as they only refer to the paranoid subtype of schizophrenia, which is also thought to start later than most other subtypes.

One of the most interesting findings, however, is the excess of women in late-onset schizophrenia. While there is an excess of men in early-onset cases (Riecher et al. 1989, 1991), in late-onset patients the gender distribution, female:male, was found to be approximately 2:1 to 4:1 in most studies (Bleuler 1943; Knoll 1952; Klages 1961; Schimmelpenning 1965; Siegel and Rollberg 1970; Berner et al. 1973; Hinterhuber 1973; Ciompi and Müller 1976; Gabriel 1978; Huber et al. 1979; Craig and Bregman 1988; Jablensky et al. 1992; Howard et al. 1993a; Castle and Murray 1993). Extreme values are 1.3:1 (Shepherd et al. 1989), on the one hand, and 6.7:1 (Pearlson et al. 1989), on the other. Only the former study, however, was based on a representative population of first admissions. The latter study, in contrast, was – as was most other studies – based on a highly selected population and included readmissions, i.e. the gender distribution could be influenced by many factors and cannot be generalized.

Results on psychopathology

As concerns symptomatology, most previous and also contemporary researchers found no or only marginal differences between late and early-onset schizophrenic diseases (e.g. Kolle 1931; Bleuler 1943; Knoll 1952; Klages 1961; Siegel and Rollberg 1970; Huber et al. 1975, 1977; Rabins et al. 1984; Jeste et al. 1988; Mayer et al. 1993; Davidson et al. 1993; Jeste et al. 1995). This does not only apply to authors who examined symptomatology cross-sectionally, but also to those who examined longitudinally in the course of the disease.

Even Kraepelin's patients, who in the beginning (1912) had shown an excess of paraphrenic clinical pictures, were shown to develop a symptomatology "which could not be differentiated from that of other patients with Dementia praecox anymore" in the later course of the disease (Mayer 1921). Furthermore, M. Bleuler (1943), who coined the term "late-onset schizophrenia", had, as already mentioned, found only a subgroup of patients differing from the classical clinical picture of early-onset schizophrenia.

In contrast to that, there are only single studies pointing to more marked differences (Pearlson et al. 1989; Howard et al. 1993a,b); however, only one of these was aimed solely at schizophrenia. Furthermore, this was a retrospective analysis of case notes only, and was restricted to a certain hospital; it was that of Pearlson et al. (1989), who compared 54 late-onset schizophrenia patients with 22 age-matched chronic and 54 young, early-onset schizophrenia patients. Late-onset cases showed significantly less thought disorder and flattening of affect, but a more colourful picture of hallucinations. The frequency of acoustic hallucinations and persecutory delusions was positively correlated with age, but not with age at onset. Even these authors finally concluded that "the phenomenologic similarities.... outweigh the differences." (p. 1572).

Howard et al. (1993a,b), who found that late- and early-onset patients were "not phenotypically homogeneous", had examined a very wide diagnostic spectrum including the over-60-year-olds with late paraphrenia and all reactive psychoses without clear exclusion criteria. The differences described by these authors (e.g. more persecutory and organized delusions and certain acoustic hallucinations in late-onset cases) could therefore at least partly be due to their sample selection.

When we examined 1109 consecutive first admissions, of all ages, with a schizophrenic or paranoid psychosis (ICD 295, 297, 298.3/4) at the Central Institute of Mental Health in Mannheim (Germany) during the years 1978–1992, we had a linear, sixfold increase in paranoid symptoms and systematic delusions from adolescence to the age group 75 years and over, whereas disorganizational symptoms, such as formal thought disorder and ego disturbances, displayed a linear decrease (Häfner et al. 1997). However, this result merely indicates that age-dependent developmental factors influence symptom formation in schizophrenia and paranoid disorders. They do not point to late- and early-onset cases representing differing disease entities.

If one considers only those studies restricted to classical late-onset schizophrenia, the few psychopathological differences described between them and early-onset patients can be summarized as follows:

In accordance with Kraepelin's earlier work some authors describe an association between late-onset and *paranoid symptomatology* (e.g. Bleuler 1943; Huber et al. 1975; Angst 1973). Pearlon's study (1989) would, however, imply that this is not so much due to the higher age of onset, but is instead due to the higher age itself. Some authors also described the *delusions* of late-onset patients as more concrete, organized and psychologically understandable (e.g. Klages 1961). Based on this finding Klages (1961) states "age ... undoubtedly has a symptom-colouring, pathoplastic influence on the psychosis" (p. 89).

In the course of the disease some authors, e.g. Marneros et al. (1992), found a higher frequency of delusions; Huber et al. (1975, 1977) found more primary delusions. *Hallucinations* are described as slightly more frequent in late-onset patients (Huber et al. 1975, 1977; Marneros et al.

Table 1 Clinical and epidemiological studies on classical late-onset

Authors	Patients examined		Diagnostic criteria of schizophrenia	Kind of investigation
	Total/late onset (*n*)	Selection of patients		
Kraepelin (1919)	1054/61	?	Dementia praecox without paraphrenia	Clinical cross-sectional
(1913)	?/78		Paraphrenia	Cross-sectional
Kolle (1931)	889/142	Cases of Carl Schneider	Schizophrenia and paraphrenia	Clinical with follow-up
	182/33	All cases of 1 year in 1 hospital	Schizophrenia and paraphrenia	Clinical cross-sectional
M. Bleuler (1943)	Clinical study ?/130	Nonsystematic: schizophrenics "who got known to me"	Schizophrenia according to Bleuler	Follow-up by Bleuler personally
	Calculations of frequencies 459/68	"Patients in asylum"	Schizophrenia according to Bleuler	Cross-sectional
	300/51	All schizophrenics of a certain hospital	Schizophrenia according to Bleuler	
Knoll (1952)	?/114	Female inpatients of a university hospital	"Delusional psychosis of menopause"[b] (paranoid schizophrenia)	Direct clinical and retrospective case-note assessment
Müller (1959)	(101)/30[a]	All schizophrenic inpatients aged > 65 years at a fixed day	"Schizophrenia according to Bleuler"	Direct, cross-sectional
Klages (1961)	?/53	All admissions with "late onset" of a university hospital in 4 years	Schizophrenia with first-rank symptoms, M. Bleuler's criteria for late-onset schizophrenia	Direct interviews and different sources of information; follow up: several years
Funding (1963)	148/5	All first admissions of a certain hospital in 14 years with onset of paranoid delusions after age 50 years	"Schizophrenia"	Direct examination and catamnesis of 1–15 years, different sources of information
Schimmelpenning (1965)	?/117 (82)[c]	All inpatients of a university-hospital in 5 years	Broad (schizophrenia, schizoform psychosis, paranoid reactions)	Direct, different sources of information, catamnesis of > 5 years
Retterstøl (1966)	84/14	All first admissions of a certain hospital with paranoid psychosis from 2 periods	Paranoid schizophrenia criteria of Langfeldt (1960)	Direct with follow-up; different sources of information
Post (1966)	(93)/34[a]	3 samples of "peristent persecutory states", > 60 years at admission	First-rank symptoms	Partly retrospective, partly follow-up
Siegel and Rollberg (1970)	?/60	All inpatients of a university-hospital in 10 years	"Schizophrenia" not specified	Clinical/case notes, details not given
Sternberg (1972)	?/487	Outpatients of a certain clinic, > 60 years	"Schizophrenia" (russian diagnosis)	Details not given
Angst et al. (1973)	291/101	Consecutive admissions in 7 hospitals in 5 countries	Only paranoid subgroup of schizophrenia (ICD 295.3)	Exact documentation, details not given
Berner et al. (1973)[d] and Gabriel (1974 a, b, 1978)[d]	311/110	Basis: all patients of a university-hospital first admitted between age 40 and 65 years, follow-up at a mean age of 77 years (only 1/5 of patients could be traced)	Late-onset schizophrenia according to M. Bleuler (1943)	Direct, duration of catamnesis > 20 years in 73% of cases
Hinterhuber (1973)	157/39	All first admissions of a university-hospital in 5 years (between 1930 and 1940)	Rediagnosis of schizophrenia from case notes according to E. Bleuler's (1908) criteria	Case notes and direct, different sources of infomation duration of catamnesis 30–40 years

Schizophrenia: methodological problems

Onset of disorder		Exclusion criteria/ exclusion diagnoses	1. Representative sample? 2. First episode/ first admitted?	Remarks
Definition	Age limit (years)			
?	> 40	?	1. No 2. No	Coined the term "Dementia praecox" because of onset in youth and poor prognosis
?	> 30	?	1. No 2. No	Mayer et al. (1921) showed that 50 of the 78 later had developed classical Dementia praecox
?	> 40	Pure paranoid disorder	1. No 2. No	Found them similar to early-onset cases
First admission	> 40	Pure paranoid disorder	1. No 2. No	
?	> 40	Amnestic syndrome and physical disease with suspected brain disturbance	1. No 2. No	Cases and their relatives from several institutions and countries, 17 already dead; coined the term "late-onset schizophrenia" as half of those with onset > 40 years showed a"characteristic symptom colouring"
?	> 40	Amnestic syndrome and physical disease with suspected brain disturbance	1. No 2. No	
	> 40	Amnestic syndrome and physical disease with suspected brain disturbance	1. Hospital prevalence 2. No	
First paranoid disorder	> 40	Organic symptoms Psychoreactive psychosis	1. No 2. No	Found them to be a subgroup of schizophrenia
First psychotic symptoms	> 40	None	1. No 2. No	Only 9 of 30 had no organic brain pathology
"Onset"	40–60	Onset > 60 years, "cerebral-organic colouring", paraphrenia, paranoid reactions	1. No 2. No	No empirical control group, but found them "similar to early-onset schizophrenia"
Beginning of paranoid delusions	> 50	Organic brain syndrome	1. No 2. Yes	In only 5 of the 148 paranoid patients could diagnosis of schizophrenia be confirmed
First paranoid symptoms	> 40	Suspected organic psychosis, depressive delusions	1. No 2. No	In 67 patients the diagnosis of schizophrenia was not confirmed due to organic deterioration or lack of chronicity
First admission	> 40	Affective psychosis, confusional state	1. No 2. Yes	Study not mainly aimed at late-onset schizophrenia
Onset of paranoid symptoms	> 50	Affective disorder	1. No 2. No	34 of the 93 patients had first-rank-symptoms, 33 organic brain pathology
?	> 40	Organic psychosis	1. No 2. No	No empirical control group
?	?	Organic brain pathology allowed	1. No 2. No	Many details missing
"Onset"	> 40	?	1. No 2. No	Markedly smaller proportion of late-onset cases in catatonic and schizoaffective psychosis
First admission	> 40	None	1. No 2. Yes	Many patients dead All patients with progressive course after age 65 years had marked organic brain pathology
First psychotic symptoms; if onset insidious: first admission	> 40	Not from Tirol, organic psychosis, no safe diagnosis based on case notes	1. No 2. Yes	One of the few who discusses the validity of retrospective diagnoses based on case notes

Table 1 (continued)

Authors	Patients examined		Diagnostic criteria of schizophrenia	Kind of investigation
	Total/late onset (*n*)	Selection of patients		
Huber et al. (1975/1979)	644/110; survivors: 502/70	All admissions of 1 university-hospital in 14 years	Schizophrenia diagnosis according to K. Schneider 1957, late-onset criteria according to M. Bleuler (1943)	Retrospective, mean duration of catamnesis 17.8 years, (including prodromi 20,7 years), sources of infomation?
Rabins et al. (1984)	(35)/21[a]	Nonsystematic, persistent delusional disease with onset > 44 years	Schizophrenia according to DSM-III without age limit	25× direct with follow-up, 10× retrospective case-note analysis
Marneros and Deister (1984)	1208/170	All first admissions of a university-hospital during 30 years	Schizophrenia clinical diagnosis according to K. Schneider (1957)	Analysis of case-notes with own standardized instrument
Jeste et al. (1988)	?/36	"Typical" patients of 4 centres	Schizophrenia: late onset according to DSM-III-R	Comparison of clinical data, details not given
Craig and Bergman (1988)	(658)/32[a]	All schizophrenia inpatients > 65 years of a state mental hospital during 5 years	DSM-III	Longitudinal case-note analysis
Pearlson et al. (1989)	?/54	All admissions of a hospital during 5 years with onset > 45 years	DSM-III-R schizophrenia	Longitudinal case-note analysis, comparison with 22 age-matched early-onset and 54 young schizophrenic patients
Marneros et al. (1992)	148/12	Admissions of 2 university-hospitals during 30 years	Schizophrenia according to K. Schneider (1957)	Case notes and direct, all sources of information, mean duration of catamnesis 27 years
Häfner et al. (1993a, b)	276/(76)[e]	All first admissions of a defined catchment area during 2 years	ICD-9: 295, 297, 298.3 + 4	Direct with follow-up and follow-back, all sources of information
Howard et al. (1993a) Castle and Murray (1993)	470/134	All first contacts with psychiatric services (in- and outpatients) in defined catchment area and 20 years	ICD-9: 295, 297.2, 298	Case-note analysis with standardized instruments, patients ascertained by case register
Mayer et al. (1993)	1371/130	All first admissions of a hospital in 4 years (onset in the 2 years beforehand)	ICD-9: 295, 297	Clinical routine documentation (AMDP), cross-sectional
Yassa and Suranyi-Cadotte (1993)	(40)/20	All patients > 65 years old admitted to a psychogeriatric ward within 7 years	DSM-III-R	Direct with follow-up and follow-back
Jeste et al. (1995)	64/25	Nonsystematic, patients from different medical centres and private physicians	DSM-III-R	Direct clinical and neuropsychological assessment with follow-back

NOTE: Considered are only studies on *schizophrenia* with late onset, not studies to "late paraphrenia" or "paranoid disorders", which do not differentiate between schizophrenic and non-schizophrenic patients; neither have case reports or studies restricted to aetiological questions (e.g. CT or MRT studies) been listed

[a] Total number of examined is in parentheses if the number did not refer to the schizophrenic patients of all age groups, but the study population consisted of elderly patients of different diagnostic categories

1992) and as present in more sensory modalities (Pearlson et al. 1989). Especially described are more tactile (Klages 1961) and olfactory hallucinations as well as hallucinations of taste (Huber et al. 1975, 1977), and also a characteristic "verbal hallucinosis" (Schimmelpenning 1965).

Thought disorders, on the other hand, have been described to be less frequent by Pearlson et al. (1989). Jeste et al. (1988) only found a lower prevalence of looseness of association, and Marneros et al. (1992) comparably less incoherence in late-onset cases.

As concerns *affective symptomatology*, some authors have reported depressive prodromal episodes in late-onset patients (e.g. Stransky 1906; Kolle 1931; Klages 1961; Siegel and Rollberg 1970). But they have not examined, if

Onset of disorder		Exclusion criteria/ exclusion diagnoses	1. Representative sample? 2. First episode/ first admitted?	Remarks
Definition	Age limit (years)			
?	> 40	Organic Clinical picture, organic brain disorder	1. No 2. No	Found slightly more paranoid and paranoid hallucinatory delusions in late- as compared with early-onset cases
Beginning of persistent delusions	> 44	Affective disorder, cognitive disturbance (Mini-Mental State)	1. No 2. No	Diagnosed 21× schizophrenia, 11× schizophreniform disorder and 3× paranoia; found late-onset similar to early-onset cases
First admission	> 50	Not German speaking	1. No 2. Yes	Found more delusions and hallucinations but less thought disorder in patients with onset > 50 years, as opposed to < 50 years
"Onset"	> 45	Organic brain disorder, affective disorder, etc., according to DSM-III-R	1. No 2. No	Four highly selected samples from 4 different centres: only one sample was compared with early-onset cases
"Onset"	> 45	Affective disorder, organic brain disorder	1. No 2. No	Schizophrenia diagnosis confirmed in only 25%, 40% organic deterioration, 20% affective disorder, 15% full remission
Age at first positive symptom	> 45	Organic brain disorder	1. No 2. No	Only one rater, no test of reliability; found less thought disorder and affective flattening in late-onset cases, but more persecutory delusions
"Onset"	> 45	Organic psychosis, schizoaffective psychosis, affective psychosis	1. No 2. No	Part of a bigger study on 402 of originally 950 patients with functional psychoses
First admission	> 35	Suspected organic brain pathology, mental handicap	1. Yes 2. Yes	Comparison of three age groups: 12–24, 25–34, 35–39 years
First treatment or begin of subjective distress or impairment	> 45	Organic basis of disorder	1. Yes 2. Yes	Very broad diagnostic spectrum; found late- and early-onset cases "psychopathologically *not* homogenous"
"Onset"	40–63	Organic brain disorder	1. No 2. Yes	Comparison of extreme age groups: 40–63 vs 18–23 years
"Active symptom"	> 45	Evidence of organicity in tests, conditions that many mimic schizophrenia	1. No 2. No	Comparison of 20 late-onset schizophrenic with 7 paraphrenia patients and 13 patients with paranoia
Onset of psychotic symptoms	> 45	Psychosis secondary to substance abuse or dementia	1. No 2. No	Comparison of 25 late-onset with 39 early onset schizophrenic and 35 healthy subjects

[b] Special category of Knoll (1952)
[c] Only 82 were examined directly, 15 of them late-onset schizophrenia patients
[d] Subgroup of the study by Ciompi and Müller (1976)
[e] Number in parentheses as the age boundary was at 35 years in this study

or to what extent this phenomenon is also present in early-onset patients. Regarding the symptomatology of the illness itself, some authors since Stransky (1906) have reported a comparably well-preserved affectivity in late-onset schizophrenia patients. Bleuler (1943) found less affective flattening, Pearlson et al. (1989) less inappropriateness of affect, Huber et al. (1975) and Jeste et al. (1988) less depressive mood – Huber et al., however, at the beginning of the disesase only and not anymore in its further course. On the other hand, Klages (1961) and Mayer et al. (1993) found comparably more depressive symptoms in late-onset cases. However, when Mayer et al. excluded paranoid psychoses and analysed only the schizophrenic ones, these differences disappeared. The

only persisting difference then was a higher score in the "autonomic syndrome" with more vegetative symptoms in late-onset cases.

Negative symptoms have been described to show an inverse association with age by Andreasen et al. (1990), but they have analysed a group of under-46-year-old patients only. In only one study have age differences between late- and early-onset cases been described, as concerns negative symptoms. This again is the study by Howard et al. (1993a), i.e. the differences are probably due to their patient selection.

Results on course

Studies on the course of late-onset schizophrenia are rare, although age has been analysed as an influencing factor in various studies on the course of schizophrenia in general. The results of these latter studies are inconsistent; details are given, for example by Watt and Szulecka (1979) or Häfner and Hambrecht (1994). Neither these studies, nor those on late paraphrenia, nor those on the later course of early-onset patients are considered here. (For reviews concerning these patients see, e.g., Ciompi 1987; Harris and Jeste 1988; Gurland 1988; Häfner and Hambrecht 1994). This review is instead restricted to the course of late-onset schizophrenia itself. Methodological details of the studies have been given in Table 1.

M. Bleuler (1943) was again one of the first to examine the course of late-onset schizophrenia and found that these patients, as compared with early-onset patients, less often end up with severe dementia, but more often with a "mild state of deficiency" and that a comparable proportion experiences "social healing". Also, most other early German researchers describe a relatively benign prognosis in late-onset cases (e.g. Klages 1961; Siegel and Rollberg 1970), although early-onset cases were never directly compared on an empirical basis.

On the other hand, there were several authors who did not confirm this. Thus, for example, Schimmelpenning (1965) or Berner et al. (1973) found a preponderance of uniformly chronic courses in late-onset schizophrenia. In Berner's population only 13% of the patients with onset between 40 and 65 years could be said to be "healthy", when they were reexamined at an average age of 77 years. Gabriel (1974a, 1978) assessed the psychosocial adaption in the same population and describes it as very poor in approximately one third of patients.

Hinterhuber (1973) and Huber et al. (1975,1977) were the first to compare late- with early-onset cases directly on an empirical basis. Hinterhuber (1973) found a definitely *poorer* course in the late-onset cases: after a catamnestic period of 30–40 years only 16% of them were cured and 40% suffered from severe psychotic disturbances, whereas 63% of the patients with onset before age 20 years had completely recovered and only 12% of them suffered from a "severe deficiency syndrome". Huber et al. (1975,1977) in contrast found a milder course in late-onset schizophrenia. After a catamnestic period of on average 17.8 years, they found that 30% of the late-onset as opposed to only 22% of all schizophrenic patients had completely remitted. Only Hinterhuber's (1973) study, however, was restricted to *first* admitted.

Only few studies on the course of classical late-onset schizophrenia have been conducted by Anglo-American authors. Fish (1960), Blessed and Wilson (1982) and Rabins et al. (1984) have examined small samples of diagnostically mixed patient groups which cannot easily be interpreted. Craig and Bregman (1988) conducted a chart review of 32 patients aged 65 years or older with onset of symptoms after age 45 years, who met DSM-III criteria for schizophrenia (except age of onset). Clinical course over 7 up to 11 years revealed only 25% to follow an unequivocally schizophrenic pattern, whereas 40.6% showed signs of organic deterioration.

Holden (1987) only describes patients with late paraphrenia occurring for the first time after age 60 years. His study, nevertheless, must be mentioned, since he found that after a course of 10 years only 10% of his 47 patients could still be diagnosed as "schizophreniform". The other patients had to be classified as schizoaffective, paranoid, organic, symptomatic or affective at follow-up. This study confirms that late paraphrenia has to be considered as different from late-onset schizophrenia and probably as a whole "spectrum of overlapping conditions with paranoid delusions" (Holden 1987, p. 635). Also, more recent studies indicate that late paraphrenia is distinct from late-onset schizophrenia and that an organic substrate probably exists in many cases of late paraphrenia, whereas gross organic pathology cannot be detected in late-onset schizophrenia (Naguib 1991; Howard et al. 1994; for review see Riecher-Rössler et al.1995).

Own studies

Methods

First study

Incidence, gender distribution and symptomatology of late-onset schizophrenia have been examined in the framework of the ABC study (Häfner et al. 1991a, 1993a,b), where we could examine a representative population of first admitted using standardized diagnostic criteria and instruments and an operationalized definition of onset. We screened all patients who were admitted to any of the ten mental hospitals and units caring for the population of a large, defined catchment area of 1.5 million inhabitants (Mannheim, Heidelberg, Rhine-Neckar district and eastern Palatinate) during a period of 24 months between 1987 and 1989. Further inclusion criteria were: first admission with the clinical diagnosis of schizophrenia (ICD-9:295) or paranoid psychosis (ICD-9:297) or acute paranoid reaction (ICD-9:298.3) or psychogenic psychosis with paranoid symptoms (ICD-9:298.4; WHO 1978), German citizenship, main residence in catchment area, age between 12 and 59 years and absence of organic brain disease or severe mental retardation.

A total of 392 patients fulfilled our inclusion criteria; 116 (29.6%) refused or were missed because of very short hospital stays. In the case of 9 additional patients, not all interviews could be obtained. A total of 267 patients could be examined with our whole set of instruments (see below). Demographic data and the clinical diagnosis according to ICD-9 were known for all 392 patients from clinical routine documentation.

As concerns incidence and gender distribution, our results are based on the whole population of 392 patients, and as concerns symptomatology, on the 267 patients fully examined. A comparison of the 267 fully examined with all 392 patients showed that among the patients fully examined, there was a slightly higher proportion with the narrower diagnosis of schizophrenia (ICD-9: 295 87.6% vs 80.0%, $p < 0.05$) and they were slightly younger (30.5 vs 33.0 years, $p < 0.05$). Further details about the sample are given by Häfner et al. (1991a, 1993a,b).

Symptomatology at admission was assessed using the Present State Examination (PSE: Wing et al. 1973, 1974), the SANS (Scale for the Assessment of Negative Symptoms; Andreasen 1981), and the PIRS (Psychological Impairment Rating Schedule; Jablensky et al.1980). For an exact assessment and operationalization of the onset of the disease we used the IRAOS (Instrument for the Retrospective Assessment of the Onset of Schizophrenia; Häfner et al. 1992a). This is a semistructured instrument which allows the assessment of the early preclinical course of schizophrenia on different levels such as prodromi, first signs, symptoms and social indicators of the beginning mental disease. In 171 cases also significant others could be interviewed using the DAS (Disability Assessment Schedule). All interviews were conducted by specially trained psychiatrists and clinical psychologists. Diagnoses were based on the PSE and confirmed by the computer programme CATEGO (Wing et al. 1973, 1974).

All analyses were performed once for schizophrenia (ICD-9:295) only (restrictive diagnostic definition) and once for all patients (ICD-9: 295; 297; 298.3+.4, broad diagnostic definition).

Second study

Regarding the course of late-onset schizophrenia we analysed a representative case register cohort of all 1423 Danish patients first admitted in 1976 with a diagnosis of a schizophrenic, paranoid or paranoid reactive psychosis or borderline state (ICD-8: 295; 297; 298.3; 301.83; WHO 1967) over the course of 10 years. Inclusion and exclusion criteria were the same as in the above-described ABC study.

Results

Age-related risk

In the ABC study (Häfner et al. 1993a,b), which had an upper age limit of 60 years, 76 (19.4%) of all 392 patients with a schizophrenic or paranoid psychosis, or 52 (15.6%) of the 334 schizophrenia patients, respectively, were first admitted as late as between age 40 and 59 years. The proportion of patients with onset after age 60 years had to be estimated on the basis of a not fully representative sample of consecutive first admissions of the same diagnostic definition at the Central Institute of Mental Health, Mannheim, where we could analyze all patients without an upper age limit over an admission period of 14 years (n = 1109). (Data courtesy of W. Häfner-Ranabauer.) Estimations based on this clinical population suggested an additional 3–4% of first admissions with the above-named diagnoses after age 60 years.

The fact that in the ABC study we assessed all first admissions from a defined catchment area with a defined population size also allowed us to calculate age-specific incidence rates. They were found to be three to four times as high in the age group 12–39 years as in the age group 40 to 59 years. Thus, for the restrictive diagnostic definition of schizophrenia (ICD 295) the yearly incidence rate was 23 cases per 100000 inhabitants in the age group 12–39 years, whereas in the age group 40–59 years it was only 6.5/100000. Corresponding figures for the broad diagnostic definition (including ICD 295,297,298.3+.4) are given in Table 2.

Table 2 Yearly incidence rates of late-onset schizophrenia by gender and broadness of diagnostic concept (ABC study)

Age group (years)	Schizoprenia and paranoid disorder (ICD-9: 295, 297, 298.3+ .4)[a]	Schizophrenia only (ICD-9: 295)[a]
Men (n = 187)		
12–39	26.1	24.2
40–59	6.0	4.2
12–59	18.2	16.4
Women (n = 205)		
12–39	25.2	21.7
40–59	13.1	8.9
12–59	20.5	16.6
Total (n = 392)		
12–39	25.7	23.0
40–59	9.5	6.5
12–59	19.4	16.5

[a] Rate per 100000 inhabitants and year

As regards gender distribution, only 12.8% of the male, but 25.5% of the female, patients had their first admission for a schizophrenic or paranoid psychosis when they were 40 years or older. Restricting the analyses to schizophrenic patients (ICD 295) only, the corresponding figures were 10.1 and 21.1%, respectively. This ratio of approximately 2:1 (female:male) could also be confirmed based on incidence rates (see Table 2).

In previous studies we had already shown that the morbidity risk of women does not simply continuously decrease with increasing age (Häfner et al. 1989, 1991a, 1993a,b). Rather the women have a second peak of illness onset after age 45. In order to explain this phenomenon we have conducted systematic investigations (Häfner et al. 1989, 1990b, 1993a,b). At first we tested if psychosocial factors with age- and gender-specific distribution, such as family status or occupational status, were influencing age of first admission. The results were largely negative (Häfner et al. 1989; Riecher-Rössler et al.1992). To explain the gender differences in age at onset rather a biological hypothesis gained increasing evidence on the basis of our epidemiological (Häfner et al. 1989, 1991a, 1992b, 1993b) and clinical studies (Riecher-Rössler et al. 1994) as well as animal experiments (Häfner et al. 1991b): the so-called oestrogen-hypothesis. This suggests that oestradiol can enhance the vulnerability threshold for the outbreak of schizophrenia, probably mainly by its antidopaminergic properties known from basic and animal research (e.g. Gordon et al. 1980; DiPaolo et al. 1981; Bédard et al. 1984; DiPaolo 1994; for review see Seeman 1981; Riecher-Rössler and Häfner 1993). If this hypothe-

Table 3 Psychopathology scores with significant differences between early- and late-onset schizophrenia cases (ICD-9: 295) by gender (ABC study). *TOT* total score of PSE (Wing et al. 1973, 1974); *NSN* non-specific neurotic syndromes, subscore of PSE; *DAH* delusions and hallucinations, subscore of PSE

	Men[a]			Women[b]			Total[c]		
	M	(SD)	p(t)	M	(SD)	p(t)	M	(SD)	p(t)
TOT									
< 40 years	42.5	(16.4)	**	41.9	(16.1)	n.s.	42.2	(16.2)	○
≥ 40 years	24.6	(14.8)		39.5	(14.5)		35.9	(15.7)	
NSN									
< 40 years	16.1	(7.3)	**	15.1	(6.1)	n.s.	15.6	(6.8)	**
≥ 40 years	8.3	(5.4)		12.9	(6.1)		11.8	(6.2)	
DAH									
< 40 years	10.6	(7.3)	**	11.4	(7.7)	n.s.	11.0	(7.5)	n.s.
≥ 40 years	5.3	(3.3)		11.7	(7.8)		10.1	(7.5)	
Psychotic symptoms									
< 40 years	10.7	(5.5)	○	11.3	(4.8)	n.s.	11.0	(5.2)	n.s.
≥ 40 years	7.1	(3.9)		11.1	(4.8)		10.2	(4.8)	
First-rank symptoms									
< 40 years	2.2	(2.0)	○	2.3	(1.9)	n.s.	2.2	(2.0)	n.s.
≥ 40 years	0.7	(1.3)		2.0	(1.8)		1.7	(1.8)	

n.s. not significant; ○ $p \leq 0.1$; ** $p \leq 0.01$
[a] $n < 40$ years: 106; $n \geq 40$ years: 7
[b] $n < 40$ years: 99; $n \geq 40$ years: 22
[c] $n < 40$ years: 205; $n \geq 40$ years: 29

sis were valid, women would be protected from the outbreak of schizophrenia to a certain degree from puberty until (pre-)menopause, i.e. during their period of life with a high physiological oestradiol production. Only when oestradiol levels slowly decrease – and this begins already approximately 5 years before actual menopause which occurs at a mean age of approximately 51–52 years (Labhart 1978) – this protective factor would slowly disappear and women would "catch up" with their morbidity risk. This could at least partly explain women's second peak of illness onset after age 45 years, and thereby also the excess of women in late-onset schizophrenia.

Psychopathology

Forty-three of the 267 patients fully examined were 40 years or older when they had their first admission with a schizophrenic or paranoid psychosis (ICD-9: 295, 297, 298.3+.4; WHO 1978). The symptomatology of these patients was surprisingly similar to that of the 224 early-onset patients, and this was true for the whole group of schizophrenic and paranoid patients, but also if one looked at the schizophrenic patients separately. Data are in the following given for the the schizophrenia patients (ICD 295) only.

In a first step we analysed the PSE total score and its four subscores DAH (Delusions and Hallucinations), BSO (Behaviour, Speech and other Syndromes), SNR (Specific Neurotic Syndromes) and NSN (Nonspecific Neurotic Syndromes) as well as the global scores of the SANS (Scale for the Assessment of Negative Symptoms), the PIRS (Psychological Impairment Rating Schedule) and the DAS (Disability Assessment Schedule). Late-onset patients merely had less nonspecific neurotic symptomatology (NSN 11.8 vs 15.6, $p < 0.01$) and therefore slightly lower scores of total psychopathology (PSE total score TOT 35.9 vs 42.2, $p < 0.1$, see right column of Table 3). The two age groups did not, however, show significant differences in any of the other scores. Especially there were no significant differences in their psychotic symptomatology. This was also true on the level of syndromes and symptoms: Only 15 of 104 PSE symptoms showed significant differences between late, and early-onset patients. In addition, apart from the fact that all significanct differences disappeared with alpha correction, none of the differing symptoms was a psychotic one. Late-onset patients instead had slightly lower scores in several unspecific symptoms such as "delayed sleep", "derealization", "simple ideas of reference" or "neglect through brooding". Even the mean number of psychotic symptoms and the mean number of first-rank symptoms were the same for both age groups (Table 3). The schizophrenic "nuclear syndrome" according to the standardized diagnostic system CATEGO, which is mainly defined by the presence of first-rank symptoms, was present in 58.6% of the late-onset and in 68.3% of the early-onset cases – a difference which also did not reach statistical significance. In a discriminant analysis based on different psychopathology scores only 60.4% of the schizophrenia patients could be correctly classified as belonging to the early- or late-onset group (Wilks' lambda = 0.954, $df = 2$, $p < 0.05$), which was almost entirely due to the difference in nonspecific neurotic syndromes.

As further analyses showed, even the few differences in symptomatology have to be explained at least partly by pathoplastic influences of age and age-associated characteristics (Riecher-Rössler et al., in preparation). We thus did not find any hints on late-onset schizophrenia being a distinct entity or subgroup of schizophrenic disorders, which would justify a special term or even diagnostic category for them.

In a further step we looked at the genders differentially. Based on the oestrogen hypothesis and on our finding that

Table 4 Total duration of hospitalizations during 10-year course after and including index admission, independent of diagnoses at readmissions, Denmark, 1976. NOTE: Index admission is first admission with the diagnosis of a schizophrenic or paranoid or paranoid reactive psychosis or borderline state (ICD-8: 295, 297, 298.3, 301.83). All analyses were performed after exclusion of those who had died during the 10 years

	< 40 years			40–59 years			≥ 60 years			Total			p^b
	n	M	(SD)	*n*	M	(SD)	*n*	M	(SD)	*n*	M	(SD)	
Schizophrenia[a] (ICD 295)													
Men	181	718	(863)	51	315	(630)	8	300	(296)	240	618	(823)	**
Women	114	565	(630)	71	514	(840)	22	499	(678)	207	541	(711)	n.s.
Total	295	659	(784)	122	431	(763)	30	446	(602)	447	582	(773)	*
p(t)		○			n.s.			n.s.			n.s.		
All diagnoses[a] (ICD 295, 297, 398.3, 301.83)													
Men	335	579	(772)	125	232	(536)	24	128	(209)	484	467	(719)	***
Women	302	424	(577)	289	278	(566)	85	440	(846)	676	364	(616)	**
Total	637	506	(690)	414	264	(557)	109	371	(763)	1160	407	(662)	***
p(t)		**			n.s.			**			**		

[a] Diagnosis at index admission
[b] Analyses of variance: *n.s.* not significant; ○ $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

oestrogen might not only elevate the vulnerability threshold for the onset of schizophrenia and schizoprenic relapses, but also slightly attentuate schizophrenic symptomatology (Riecher-Rössler et al. 1994a,b), we formulated the following hypothesis: women after the loss of this protective factor in (pre)menopause should not only present an excess of illness onsets, but also more severe forms of the disease. Our findings seem to support this hypothesis: symptomatology of late-onset women proved to be distinctly severer than that of late-onset men (Table .3). The few late-onset men not only showed a lower total score of pychopathology (mean PSE total score, $p < 0.05$), but also suffered from fewer delusions and hallucinations (DAH, $p < 0.01$), fewer nonspecific neurotic syndromes (NSN, $p < 0.1$), and fewer psychotic ($p < 0.05$) and first-rank symptoms ($p < 0.1$). Late-onset women were in contrast to that in most areas almost as severly disturbed as the early-onset patients of both genders (see Table 3).

Course

As concerns the course of the disease, own analyses have thus far only been done on case register data, i.e. on the institutional course of late-onset as compared with early-onset patients. We examined the 10-year course of a cohort of 1423 Danish patients (second study). Of these patients, 536 at this "index-admission" belonged to the narrow diagnostic group of schizophrenia (ICD: 295), the other 887 to the related diagnoses, i.e. paranoid or paranoid reactive psychosis or borderline state (ICD-8: 297, 298.3, 301.83; WHO 1967).

Seven hundred thirty-four (51.6%) of all patients and 212 (39.6%) of the schizophrenic patients had their index admission at age 40 years or later. This comparatively high proportion of late-onset cases might be explained by the fact that 394 (27.7%) of the patients had already been admitted with another diagnosis before this index admission – a finding, which is well in accordance with the fact that the schizophrenia diagnosis is given only quite restrictively in Denmark (Munk-Jørgensen 1985; Häfner et al. 1989; Löffler et al. 1994).

Comparing the patients with index admission before age 40 years with those first admitted thereafter, the institutional course was found to be much better in the late-onset cases. This was true for the schizophrenic patients only, but also when the analyses included all patients. Because of the narrow diagnostic concept in Denmark, figures are in the following given for all patients including related diagnoses. Findings on narrowly defined schizophrenia (ICD-8:295) were very similar. The mean number of hospitalizations over the 10-year course was only 2.5 (SD 2.2) in late-onset patients, but 4.1 (SD 3.4) in early-onset cases ($p < 0.001$). Also, total duration of hospitalizations was much lower in late-onset cases (mean 286 days, SD 607 days) than in early-onset cases (mean 506 days, SD 690 days, $p < 0.001$). Already after index hospitalization, the late-onset cases had a significantly longer "survival time" in the community before they had to be rehospitalized ($p \leq 0.001$, Lee-Desu statistics), and significantly more of them did not have to be rehospitalized at all. These results were also true after correcting for the differing mortality rates of the two age groups.

But even if these differences were more marked than those concerning symptomatology, we could nevertheless show that they do not indicate to late- and early-onset schizophrenia as being different entities or due to different pathogenetic processes. Instead, numerous influencing factors covarying with age were identified, which had contributed to the better course of the elderly late-onset patients. Thus, as multiple regression analysis showed the

better course of the late-onset cases among other things seems to be due to the fact that these patients are more often married than the younger early-onset ones, i.e. being married was one of the factors to reduce mean number (β: –0.063, $p < 0.05$) and duration (β: –0.107, $p < 0.001$) of hospitalizations. In contrast, patients who had had psychiatric admissions with another diagnosis prior to index admission had significantly more hospitalizations (β: 0.194, $p < 0.001$) and longer hospitalizations (β: 0.161, $p < 0.001$) over the 10-year course.

Concerning gender differences we again had very interesting results, potentially in accordance with the oestrogen hypothesis: the course of late-onset women seems to be poorer than that of late-onset men. In fact, whereas in early onset cases women over the 10 years had spent less days in hospital than men, in late- and very late-onset cases this seems to be reversed with women spending more days in hospital than men (Table 4).

Discussion and conclusion

Based on a comprehensive review of the literature it could be shown that we do not have very sound knowledge on the classical late-onset schizophrenia(s) as defined by M. Bleuler (1943) and adopted by German-language psychiatry, i.e. schizophrenia-like clinical pictures with onset after age 40 years. This is mainly due to two reasons: on the one hand, many studies on late-onset schizophrenia suffer from severe methodological limitations; on the other hand, the term and concept "late-onset schizophrenia" internationally is used very unequivocally with the consequence that many findings on so-called "late-onset schizophrenia", though cited repeatedly, are in fact not based on classical late-onset schizophrenia, but on late paraphrenia, i.e. a "spectrum of overlapping conditions with paranoid delusions" (Holden 1987, p. 635), or on mixed populations of both diagnostic groups.

Looking at classical late-onset schizophrenia only and at the methodologically sounder studies, few findings really appear to be reliable:

1. Late-onset schizophrenic disorders are much rarer than the classical schizophrenic psychoses with onset before age 40 years. Well in accordance with other authors, in our own studies only approximately 15–16% of all schizophrenic patients had their first admission with this diagnosis between age 40 and 60 years. Based on all first admissions of a defined catchment area we calculated the morbidity risk for schizophrenia being approximately 3–4 times as high before age 40 years as in the age group 40–59 years. Furthermore, late-onset schizophrenia is much more frequent in women than in men: within the age group 40–59 years the morbidity risk for women was approximately double as high as that for men. First admission after age 60 years was very rare.

2. As concerns symptomatology, most studies have not found essential differences between late- and early-onset cases. The same was true in our own study, which was one of the first to examine a representative sample of first admissions with standardized instruments, and in direct comparison to a control group of early-onset patients. Late-onset cases only showed a somewhat milder nonspecific neurotic symptomatology and as a consequence of this a somewhat lower score for total psychopathology. But there were no significant differences in psychotic symptoms. If one looked at the genders separately, however, the few late-onset men could be shown to have a distinctly milder symptomatology than the late-onset women and the early-onset patients of both genders. This was true even for the psychotic area. In contrast to that, the late-onset women's symptomatology was almost as severe as that of the early-onset cases.

3. As to the course of late-onset schizophrenia, studies are rare and their results very contradictory. Thus, conclusions can hardly be drawn. Own studies could thus far only be done on a Danish cases register population, i.e. on the institutional aspects of the course. During the 10 years after first admission for a schizophrenic or paranoid disorder, late-onset patients had significantly fewer and shorter hospital stays as compared with the early-onset cases. Eaton et al. (1992) had similar results based on case register data not only from Denmark, but also from other countries. As regards gender differences, our results are well in accordance with our results on symptomatology: the course of late-onset women seems to be poorer than that of late-onset men.

In summary, it can thus be stated that late-onset schizophrenia does not substantially differ from early-onset schizophrenia as regards symptomatology. The institutional course of late-onset cases, however, seems to be comparably milder. But this, and also the few slight differences in nonspecific symptomatology, are obviously mainly due to the fact that age and numerous age-associated characteristics have a somewhat symptom-colouring pathoplastic effect and also a positive influence on the course of the disease. We have not found any hints on late-onset schizophrenia being a separate entity or subgroup of the disease, thereby justifying the use of a separate term or even a separate diagnostic category for these late-onset cases. Instead, they seem to belong to the same (group) of diseases as the classical early-onset schizophrenia(s) with onset before age 40 years. Our results thus give additional support for the decision to omit late-onset schizophrenia as a separate subcategory in DSM-IV as opposed to the former DSM-III-R.

The fact that most late-onset patients are female, and also our finding that these late-onset women suffer from a comparatively more severe symptomatology and course, might be explained by the above-mentioned oestrogen effect: it could be speculated that oestradiol by its neuromodulatory and probably antidopaminergic properties can delay illness onset in some women until (pre)menopause, when physiological oestradiol levels drop drastically. These women would then be "unmasked" as a comparatively vulnerable population and develop a relatively severe symptomatology and course of their disease. This, how-

ever, is still speculative and further studies will have to be conducted to confirm our results and possibly also this hypothesis.

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