Summary and General Discussion
The general aim of this thesis was to foster our understanding of late life schizophrenia spectrum disorders, by studying a cohort of elderly patients with schizophrenia spectrum disorders at a descriptive level. In this chapter, the most relevant results will be summarised, integrated and discussed, along with some comments on methodological aspects of the individual studies. Finally, clinical recommendations and suggestions for future research will be presented.

**Review of social functioning (Chapter 2)**

In line with the general dearth of data on elderly schizophrenia patients (Jeste and Nasrallah, 2003), our review found a limited number of relevant publications on social functioning in older community-dwelling patients. Methodological flaws, as well as biases related to the (mostly North-American) origin of studies, further restrict the amount of robust conclusions that are to be drawn from the available literature. Nonetheless, a number of clinically relevant findings clearly emerge from our review. Without any doubt, most elderly people with schizophrenia are well behind their healthy age-peers in their social achievements, such as marital relations, friendships, employment and independent residence. Schizophrenia patients also appear to be socially disadvantaged in comparison to elderly patients with other mental illnesses, although to a lesser extent. Next, a consistent finding across studies is a marked heterogeneity in the level of social functioning. Severely incapacitated, socially isolated patients and near normal functioning, socially fairly well-integrated individuals occupy the extremes of a wide spectrum of social functioning.

The existing literature provides some evidence for the impact of factors relating to social support (network size, availability of a confidant) on the level of social functioning, but this is a strongly understudied area. More publications are available on social skills. Patients report various
Impairments in social skills, correlating with the severity of clinical symptoms. When employing observer-based measures, both clinical symptoms and cognitive abilities figure among the variables that relate to social skills, but cognitive abilities seem to outweigh psychotic symptoms.

A large part of the variance in social functioning remains unexplained. Factors such as gender and age at onset of the disorder will most likely be of relevance in this respect, but little research has been done on these variables. Finally, studies differ in their use of self-report and observer-based instruments to measure social functioning. There is a strong argument for combining subjective and objective measurements, as eventual discrepancies between these two points of view may highlight meaningful diversities in appreciation of social functioning.

**Prevalence and age at onset (Chapter 3)**

In a first approach of our study cohort, we assessed the prevalence of schizophrenia spectrum disorders in the psychiatric catchment area under investigation. In addition, we evaluated the distribution of age at onset and gender. The prevalence rate of a disorder is determined by several factors: incidence, mortality, recovery and migration (Figure 1).

In the treated patient population within our catchment area, we found a one-year prevalence rate of 0.71% for the combined disorders (schizophrenia, schizoaffective disorder, delusional disorder). Importantly, the schizophrenia prevalence rate in our study (0.55%) aligns well with the rates reported for younger schizophrenia patients (Saha et al., 2005; Perälä et al., 2007). This confirms the clinical relevance of late life schizophrenia, clearly refuting remaining beliefs that schizophrenia is reduced to a negligible presence in older age. Furthermore, this finding hints implicitly at the unique mix of elderly schizophrenia patients, when considering the age at onset of their illness. The increased mortality of individuals who have contracted schizophrenia at an early age, inevitably
leads to an accelerated shrinking with ageing of the early-onset subgroup. Therefore, the finding of a net prevalence rate similar to that in younger schizophrenia populations suggests that the outflow of early-onset patients is roughly compensated for by the inflow of a comparable number of patients with a later age at onset. This hypothesis is supported by our findings on the distribution of age at onset in our study population: of all schizophrenia patients, 36.4% were aged 40 years or older at the onset of their disorder.

Among women, the prevalence of schizophrenia was nearly two times higher than in men (0.68% vs. 0.35%). Women outnumbered men in the prevalence rates for nearly all diagnostic subgroups. While the overrepresentation of women in the late and very-late-onset subgroups is
in line with a large body of empirical data (Howard et al., 2000; Vahia et al., 2010), women also outnumbered men in the early onset subgroup. For this intriguing finding, several alternative interpretations may be considered, although all remain speculative due to the cross-sectional nature of our data. Higher attrition rates in men (Kreyenbuhl et al., 2009), as well as excess mortality in men with schizophrenia (Brown, 1997) are partially supported by the available literature, but conclusive evidence is lacking. Higher recovery rates in men compared to women are not supported by the literature (Grossman et al., 2008). A cohort effect may theoretically also come into play, as there is evidence that the incidence of schizophrenia in males was lower in study populations before 1980, compared to more recent samples (Aleman et al., 2003). Finally, we have no indications for a selective migration of men from our catchment area.

The results of our prevalence study should be kept in mind when evaluating the impressive range of publications by the large North American study groups on late life schizophrenia, since these groups publish on convenience samples of community living patients. For example, in most San Diego based studies (e.g., Folsom et al., 2009) males are overrepresented, at least partly due to the recruitment of a considerable number of patients from the psychiatric services of the Veterans Administration. Most New York City-Brooklyn based studies (Cohen et al., 2008), exclusively report on schizophrenia outpatients (51% males) with an onset before 45, who have grown old.

**Symptomatic remission** (Chapter 4)

The severity of psychotic symptoms is a clinical variable with major relevance for general outcome in schizophrenia. In elderly patients, specific research on this issue is limited. Therefore, we decided to study the actual presence and level of psychotic symptoms in the schizophrenia and schizoaffective patients within our catchment area. In doing so, we
applied the recently introduced consensus definition of symptomatic remission (Andreasen et al., 2005). Next, we evaluated the association of symptomatic remission with various clinical and social variables.

Only three in ten patients (29.4%) qualified as symptomatically remitted, a notably lower proportion than reported in two studies of convenience samples of elderly schizophrenia patients (Bankole et al., 2008; Leung et al., 2008). As our study concerns an epidemiological sample, our result is more likely to be representative of the patient population that clinicians see in everyday practice. The finding that the majority of patients were non-remitters, in spite of the assumed good quality of mental health services in the study area, demonstrates that schizophrenia is still a worryingly active disorder in older age. Both positive and negative psychotic symptoms contributed substantially to non-remission, with positive symptoms (81.9% of patients) outweighing negative symptoms (57.2% of patients) to some degree.

The high prevalence of non-remission clearly argues for active therapeutic endeavours, both pharmacological and non-pharmacological, to promote remission. In this respect, another important finding of our study is that a number of variables possibly amenable to intervention correlated significantly with symptomatic remission. Remitted patients more often adhered adequately to mental health services and scored higher on some measures of social functioning. Our cross-sectional study design precludes conclusions on the directionality of these relationships. Still, these findings are in keeping with the supposition that also in elderly patients enhancing treatment engagement and promoting social integration are cornerstones of effective mental health services, as ample evidence has demonstrated in younger patient populations (Drake et al., 2009). At the same time, this aligns well with the now widely accepted notion that, while reduction of psychotic symptoms is a justifiable aim, in most patients a broader scope is required to promote general well-being. This is underlined by another finding of our study: 46.8% of all patients
scored above the threshold for clinically relevant depression (as measured by self-report), with equal levels in remitted and non-remitted patients.

Cognitive impairment (Chapter 5)

While psychotic symptoms have been the focus of research for many decades, only more recently cognition has been recognised as another key area of dysfunction in schizophrenia and related disorders (Green et al., 2004). The robust predictive value of cognitive impairments for real-world functioning has now been firmly established in a range of studies of younger schizophrenia patients (Harvey et al., 2010). At the same time, the specificity of the cognitive deficits found in schizophrenia is questioned by research comparing younger schizophrenia and bipolar patients. Several studies reported largely quantitative cognitive differences between these two major mental disorders (Krabbendam et al., 2005; Bora et al., 2009). In older age, cognitive impairments have even more relevance, both in schizophrenia and in bipolar disorder, since ageing itself also will impact on cognition. Nonetheless, in elderly patients little research has been done in this area. We compared the cognitive abilities in the community-living schizophrenia patients of our study sample with those in a cohort of elderly bipolar I euthymic outpatients, and with those in healthy age peers. In doing so, we controlled for the state of symptomatic remission in the schizophrenia patients, as psychotic symptoms and cognition are not entirely unrelated (Domínguez et al., 2009).

We found the cognitive performances of both the schizophrenia and the bipolar patients to be significantly lower than those of the healthy controls. The large effect sizes of the differences between the patients and the controls point to the clinical relevance of these cognitive impairments. Next, cognitive impairments differed very little between the remitted schizophrenia patients and the bipolar patients, with none of the two groups structurally outperforming the other. This suggests that also in
later life the two disorders, at least at a phenomenological level, share key similarities in their trait-related cognitive deficits. Furthermore, we found that the cognitive impairments in the remitted schizophrenia patients were less severe in comparison to the non-remitted schizophrenia patients, albeit with small effect sizes.

The available literature on cognition in late life schizophrenia suggests that in the majority of patients the impact of ageing is restricted to an additive effect, meaning that age-related changes in cognition add to pre-existing cognitive impairments (Vahia et al., 2007). In contrast, for the smaller group of poor-outcome patients (most of whom are permanently institutionalized), it has been shown that cognitive deficits may exacerbate with ageing, bringing about an accelerated functional decline (Harvey et al., 2003). No plausible explanation for this discrepancy has been put forward thus far.

With regard to the theme of cognition in late life schizophrenia, the very-late-onset schizophrenia-like psychosis subgroup occupies a special position. A longstanding debate on whether this diagnosis frequently heralds a dementia course has not been concluded (Mazeh et al., 2005; Kørner et al., 2009). The British psychiatrist Robert Howard, who has published extensively on this subgroup of patients, has suggested that very-late-onset patients are most appropriately viewed as having a subtle organic phenocopy of early onset schizophrenia cases (Howard, 1999). Nonetheless, no neural substrate related to the development of such a schizophrenic phenocopy has so far come forward (Jones et al., 2005).

**Needs for care (Chapter 6)**

The emotional suffering and the disabilities that are induced by a disorder as severe as schizophrenia nearly always evoke needs for care in various life domains. In later life, the pattern of these needs is most likely to diverge from that at a younger age. On the one hand, this may be a result
of changes in the manifestation of the disorder itself, with possibly opposite consequences depending on the areas involved. For instance, lessening of the severity of positive symptoms may reduce some needs. In contrast, increase of cognitive impairments may aggravate existing needs or induce new ones. At the same time, ageing itself generally induces new care needs. The net outcome of this complex process will differ from one patient to the other. Obviously, the help and support provided by carers, both formal and informal, should ideally be attuned to the current level of care needs. In this respect, little evidence is available to inform care providers. Therefore, we chose to assess the care needs in our catchment area based sample, both from the perspective of the patient and that of the staff. In addition, we examined the association of various patient characteristics with the number of unmet needs, as reported by the patients.

We found that care needs were prevalent and heterogeneous in our study population. Patients reported on average 7.6 needs (6.1 met, 1.5 unmet), slightly lower than what was reported by their staff members (8.6 needs: 6.7 met, 1.9 unmet). The total number of care needs in our study population was at the upper end of the range reported for younger patients. This is suggestive of a limited net increase in the level of needs with ageing. Patients and staff alike reported psychological and social needs to be met less often than environmental and physical needs. The finding that most environmental and physical needs were met effectively, probably reflects the generally high standard of service provision in the Netherlands. At the same time, there is much room left to better accommodate psychosocial needs, even if these may be more difficult to address. Among the variables that correlated significantly with the total number of unmet needs, the strongest relation was demonstrated for perceived quality of life (explaining 36% of the variance in unmet needs). In younger patients, having more unmet needs has also consistently been associated with a lower perceived quality of life. While this suggests that
meeting needs may improve quality of life, up till now few studies in younger patients have been able to demonstrate such a straightforward relationship (Slade et al., 2005; Priebe et al., 2007).

Although patients and staff showed consensus on the presence of most needs, there were some discrepancies in individual need areas. Such divergences obviously may have major informational value. Apart from elucidating blind spots, they may also point to differences in appraisals by patients and staff. This may be illustrated by the need concerning ‘information on illness’, that was reported as unmet by 11% of the patients in our study against none of the staff members.

Methodology, strengths and limitations

We consider the epidemiological design of three of the four clinical studies (Chapter 3, 4, 6) in this thesis as one of its major strengths, since the employment of data from a well defined psychiatric catchment area corroborates the clinical relevance of findings. Still, some limitations to this design should be mentioned. First, findings from this catchment area can not be extrapolated straightforward to other sites. Some characteristics of our catchment area which should be kept in mind when interpreting data, are its urban location, its relatively high socioeconomic standard of living, as well as the ample availability (both financially and physically) of mental health services for the elderly. Next, of the 185 patients within the catchment area who were eligible for study inclusion, 120 actually did participate. One may speculate that inclusion of the 65 non-participants (31 not able, for instance due to severely disturbed behaviour; 34 refusing consent, often psychosis driven) would have altered some results in a more negative direction (e.g., lower rate of symptomatic remission, higher rate of unmet needs). Finally, we exclusively recruited patients who were in contact with the local Mental Health Organization. This points to the pitfall of “the clinician’s illusion”. North American research suggests
that possibly more than half of all severely mental ill individuals are not connected to mental healthcare, although this figure may be more favourable in the elderly (Kreyenbuhl et al., 2009). Specific data for the Netherlands are not available. Our study results not necessarily apply to this hidden population of persons who decline help or are overlooked by services.

We regard the extensive procedure which we designed to arrive at a best estimate of the age at onset as another major strength of this thesis. Age at onset in schizophrenia has major relevance for its clinical presentation and treatment (Howard et al., 2000; Vahia et al., 2010). A reliable assessment of age at onset is a prerequisite to evaluate its impact, when studying late life schizophrenia. Chapter 2 discusses the various pitfalls in establishing age at onset in retrospect, as well as the impact of using different criteria to define age at onset.

Another methodological aspect meriting attention relates to the diagnostic composition of our study population. Next to schizophrenia patients, we recruited patients diagnosed with schizoaffective disorder and with delusional disorder. Most studies group together schizoaffective and schizophrenia patients, as the two disorders share major similarities. We followed this line as well, except in our cognition related study (Chapter 5), where we excluded schizoaffective patients. In this study we aimed to clarify eventual differences in cognitive abilities between schizophrenia and bipolar I patients. Inclusion of schizoaffective patients might have blurred possible distinctions, as schizoaffective disorder is generally conceptualized as a disorder positioned between schizophrenia and bipolar disorder (Cheniaux et al., 2008). Within the schizophrenia spectrum, delusional disorders occupy a specific position (Marneros et al., 2010). Most individuals with this disorder stay out of view of mental health services, often reluctant to seek help and enabled to do so by their largely intact general functioning. This aligns with the small number of patients (n = 8) in contact with the Mental Health Organization in our
catchment area. In our study of symptomatic remission (Chapter 4), we excluded delusional disordered patients to avoid biasing, as the diagnostic criteria for delusional disorder (e.g., absence of prominent hallucinations, no negative symptoms) obviously would have increased their chances to qualify as symptomatic remitters.

A final methodological comment relates to the use of both self-report and observer-based instruments in our study. In our opinion, the study assessing needs for care (Chapter 6) is an example of the added value of relating the opinions of patients to those of significant others. In the past, understandable concerns about the reliability and validity of self-reports in psychotic patients have often prevented an open eye to the perceptions and appraisals of these individuals. This attitude has gone through major changes in recent decades, resulting in a nowadays widely acknowledged relevance of inclusion of the patient’s perspective (Brekke et al., 1993; de Haan et al., 2001). In this respect, one should realize that observer-based instruments are also prone to major impediments (Bellack et al., 2007).

**Synthesis**

The results of this thesis paint a subtle and diverse picture of elderly people with schizophrenia spectrum disorders. While these disorders continue their prevalence into later life, some characteristics diverge clearly from those at a younger age, as is demonstrated by the female preponderance and the sizeable number of individuals with a later onset of the disorder. Psychotic symptoms keep dominating the clinical picture in the majority of elderly patients. Nonetheless, a sizeable minority is symptomatically remitted, associated with a better adherence to psychiatric services and a higher level of social functioning. On average, the cognitive abilities of patients lag well behind those of their healthy age peers. The care needs in this patient population prove to be prevalent and heterogeneous, reflecting both disorder-bound and ageing-
related disabilities and necessities. The clinical relevance of assessing unmet needs is supported by their strong relation with the quality of life as perceived by patients. Particularly, there is a gap to be filled in accommodating needs of a psychosocial nature.

Schizophrenia and related disorders are markedly heterogeneous conditions, both in their clinical presentation and their course. At the same time, the impact of ageing also differs notably between individuals, as gerontopsychological studies have clearly demonstrated (Pot et al., 2006). The merging of these two gives rise to a prominent inter-individual variation in elderly patients with schizophrenia spectrum disorders. From a theoretical point of view, patients can be positioned within a spectrum of functioning and well-being. At the upper end of this continuum, one may encounter individuals in whom the negative impact of their psychotic disorder has been limited, and who have shown resilience in integrating their illness both emotionally and socially. When they enjoy a fair to good physical condition at the same time, they may even come close to ‘successful ageing’, a concept that has been receiving more attention in recent years (Reichstadt et al., 2010). Still, ageing successfully remains elusive for the great majority of schizophrenia patients (Ibrahim et al., 2010). At the opposite end of this assumed continuum, severely incapacitated patients will be found whose lives continue to be dominated by their psychotic disorder, both at a symptomatic level (e.g., hearing threatening voices, suffering from paranoid delusions) and in the sense of social isolation. If this combines with the misfortune of a serious physical illness or disability, they will become even more dependent on care, leading to permanent institutionalization in most cases. When the content of their psychosis withholds them from seeking or accepting help, they may lead a sorrowful life, largely out of sight of society. Although the extremes of this continuum obviously attract most attention, one should be aware that most elderly schizophrenia patients are to be found at some point in between these extremes, moving with time in one direction or
the other, depending on the course of their psychotic disorder and of their physical condition.

Although this continuum model definitely appeals by its practicality, one should appreciate that at the same time it simplifies a complex and multidimensional reality. First, there is no such thing as ‘one outcome’, but several separable aspects of functioning and well-being can be discerned in one individual. For instance, while a patient may use avoidant coping strategies in most social situations, at the same time he may thoroughly enjoy working in a sheltered workshop twice a week. Next, apart from the disorder and the ageing process, a range of other factors, many of an environmental nature, will influence outcomes. For instance, the availability of homecare may be decisive for an individual to continue living independently. The other way round, the loss of a patients’ only close friend may precipitate his institutionalization. Therefore, outcome variation is determined by a range of cause and effect conditions. Neglecting this complexity is like trying to explain the tides without noticing the moon (Strauss et al., 1987). As the variables involved in this process belong to different domains (e.g., biological, psychological, social), they are not reducible to one another. Next, there are various ways in which variables exert their influences (e.g., additive, interactive, buffering). While it may still be premature to develop a comprehensive theoretical model that adequately integrates this variety of elements, building such a model step by step will most likely prove to be rewarding (Cohen, 2003).

Taken together, the trajectories of schizophrenia in later life are complex and nuanced. While some patients unfortunately take a turn for the worse, and others remain stable, it is well conceivable that some patients experience a better quality of life than earlier on in their life (Folsom et al., 2009). Thus, schizophrenia in older age does not lend itself to stereotyping.
Clinical implications

More efforts are required to reach the sizeable amount of elderly community-living individuals with schizophrenia, who currently are not seen by mental health services. Policy makers and service providers should facilitate mental health workers to engage with these people, an effort which requires a patient and persisting attitude. Next, nursing homes nowadays harbour a considerable number of elderly schizophrenia patients (Andrews et al., 2009). Their staff often lack the skills to treat these residents optimally. Offering mental health advice through a consultation model may fill this gap.

In mental health care, treatment strategies must contain an appreciation of biological, psychological and social approaches. At the biological level, cautious albeit active psychopharmacological interventions should be considered, to promote symptomatic remission. Antidepressants too often are a neglected option, as depressive symptoms that may well respond to treatment (Zisook et al., 2009) are frequently mistaken for negative symptoms.

At the psychological level, defeatism about the ability of elderly schizophrenia patients to profit from rehabilitation strategies and from psychotherapeutic interventions needs to be overcome. In adult schizophrenia care, the diversity of treatments has greatly expanded in recent decades (Drake et al., 2009; Michon and van Weeghel, 2010), ranging from individual cognitive-behavioural therapy (e.g., learning to deal with hearing voices) to group training of social skills. Little of these gains have seeped through to old age mental health services. Yet, there are some inspiring examples of intervention studies, that demonstrate the feasibility and efficiency of offering these type of treatments to older patients (Granholm et al., 2007; Mueser et al., 2010). In the Netherlands, a group course for the elderly with severe mental disorders, using creative reminiscence techniques, has shown to be feasible and acceptable to
participants (Willemse et al., 2009).

At the social level, the supply of day care facilities that offer participants a hospitable and non-demanding social environment should be encouraged. This may serve various purposes at the same time, such as overcoming social deprivation, improving personal hygiene and promoting a healthy life style. Input of participants when developing this type of facilities, ought to be encouraged. Finally, there is a need for residential homes to expand specific accommodation for the elderly with severe mental illnesses, given the rapid growth of their numbers. In the development of such services, the specific vulnerabilities of this patient group should be taken into account, as they may run a higher risk of social isolation in these living arrangements (Depla et al., 2005).

Future research

Thankfully, a growing scientific interest in the vicissitudes of schizophrenia in later life can be witnessed. Still, there is a wide unexplored field open to researchers. Some of the many areas awaiting further examination can be inferred from this thesis. First, there is a clear need for new studies with a longitudinal perspective. These may determine the stability of outcome measures over time, and will offer the opportunity to investigate causal relationships suggested by cross-sectional studies. Next, specific characteristics of older-old schizophrenia patients merit attention, as most of the available literature focuses on the younger-old subgroup. Studies of depression in older age (Beekman et al., 2002; Stek et al., 2004) may inspire this line of research.

Furthermore, priority should be given to the strongly underestimated area of social support. Gerontological studies have provided ample evidence for the importance of social support in the elderly (Penninx et al., 1997; Cornwell et al., 2008). Studies on social support in late life schizophrenia may foster ideas for interventions. Such initiatives should
be accompanied by prospective evaluations of their effect on variables, such as level of social functioning, coping styles and quality of life. In addition, the focus of research should be broadened to the specific functions and perceived burden of informal carers, who fulfil an essential role for a sizeable minority of patients (Patterson et al., 1996).

Another area with major clinical relevance relates to the physical condition of older schizophrenia patients. Medical comorbidity substantially adds to the disease burden in schizophrenia, an observation that is corroborated by the unsettling heightened figures for morbidity (Leucht et al., 2007) and mortality (Saha et al., 2007; Brown et al., 2010). In elderly patients, this theme still is largely unexplored (Vahia et al., 2007). Finally, regarding the methodologies employed, there is a case for more qualitative research, particularly on the perspective of the patients. This may provide information not easily elicited by quantitative approaches, that tend to level out individual differences. The few published qualitative studies in this area (e.g., Auslander and Jeste, 2002; Shepherd et al., 2010) testify to this.

Closing remarks

Mary V. Seeman (born 1935), a psychiatrist and Professor Emerita at the University of Toronto, is the author of numerous articles on schizophrenia. She recently published a paper titled ‘Parallels between aging and schizophrenia’ (Seeman, 2005), a highly personal account that opens as follows: “As I grow old and struggle to cope with the infirmities of age, I marvel at the resilience of my patients who grapple with and overcome the indignities of schizophrenia. Schizophrenia research is mainly about the deficits, about the many difficulties patients face. It rarely celebrates the accomplishments of patients, their ability, on the whole, to accommodate and adapt to the constraints of their illness”. Clearly, patients do not have a choice on whether or not to deal with their schizophrenic illness, but clinicians and society
as a whole certainly do. Clinicians may overcome their prejudices about elderly schizophrenia patients, who too often are merely seen as ‘lost cases’. Society may actively seek ways to counteract the double stigma that is attached to being old and having a severe mental illness (Graham et al., 2003). Doing so, will benefit not only patients, but society itself as well.
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