CHARACTERIZATION AND DIAGNOSIS OF LATE-ONSET PSYCHOTIC

DISORDER

THE CHARACTERIZATION AND DIAGNOSIS OF LATE-ONSET PSYCHOTIC

DISORDER:

A prospective longitudinal case series

By

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Abstract

There is considerable confusion regarding the diagnosis of patients presenting with non-affective psychosis in the absence of a dementia or secondary to a general medical condition in the fifth decade and beyond. A number of different terms, diagnostic criteria and age-cut-offs have been applied to this presentation posing a challenge to clinicians and researchers alike. Despite diagnostic inconsistencies and conceptual uncertainty, a remarkably consistent clinical picture has emerged. However, many questions still remain with regards to its underlying etiopathophysiological mechanisms, treatment and prognosis, including whether it is distinct from schizophrenia and whether it might be a prelude to cognitive deterioration. Currently there is no official diagnostic designation for patients who develop a primary psychosis in late life, with patients being typically diagnosed as either schizophrenia or delusional disorder, although the validity of such a distinction has been questioned.

The following prospective longitudinal study sets out to characterize the largest known group of patients (n=102) with first-episode, late-onset (>age 40) psychotic disorder on demographic, clinical, treatment and prognostic variables. Given that one of the most contentious issues in the characterization of these patients has been that of diagnostic classification, we examined whether the currently nosological distinction of schizophrenia (SCZ) from delusional disorder (DD) has validity and/or utility. Patients were classified as either SCZ (n=47) or DD (n=55) according to DSM-IV criteria, and were then compared on a number of validators proposed as part of the DSM-V

development process. As predicted, there were no significant differences between the two groups. In conclusion, our analysis did not find the current diagnostic distinction of SCZ from DD in the late-onset population to be valid and/or useful. We recommend the use of the more general diagnostic term, "Late-Onset Psychotic Disorder", to refer to all patients who develop a primary psychosis in their forties or beyond.

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Introduction

The study of non-affective psychosis presenting for the first time in the fifth decade and beyond and occurring in the absence of dementia or what is judged to be a directly, etiologically relevant medical or neurological condition, has long been hampered by diagnostic confusion. The situation of inconsistent and seemingly arbitrary terminological designations, each with its own age cut-off (e.g., 40, 45 or 60 years and above) and 'essential' clinical features, for patients who develop psychosis in later life has been present since the inception of modern-day psychiatry. The terms "presenile delusional insanity", "late-onset schizophrenia", "late paraphrenia", "persistent persecutory states of the elderly", "(late-onset) delusional disorder", "(late-onset) paranoid psychosis", "very-late-onset schizophrenia-like psychosis" and "late-onset schizophrenia disorders" is an incomplete list of designations used to refer and categorize primary psychosis which begins later in life (Kraepelin, 1904; Bleuler, 1943; Kay & Roth, 1961; Post, 1966; Evans, Paulsen, Harris, Heaton & Jeste, 1996; Riecher-Rössler, Häfner, Häfner-Ranabauer, Löffler, & Reinhard, 2003; Howard, Rabins, Seeman, Jeste & the International Late-Onset Schizophrenia Group, 2000; Palmer et al., 2003). Interestingly, despite this array of terminological usages across studies, a rather consistent clinical picture has emerged. For example, patients with late-onset psychotic disorder are more likely (i) to be female, (ii) have a relatively high level of pre-morbid and post-onset functioning, and (iii) to display an absence of thought disorganization, significant negative symptoms or catatonia. These reflect some of the notable differences between late-onset psychosis and early-onset schizophrenia, although similarities between the two

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groups also exist in terms of the extent of social isolation, associated depressive symptoms and certain neuroimaging findings. Knowledge of pathobiological underpinnings, best treatment practice, prognosis and the relationship to the development of dementia is lacking for the late-onset age group. In addition to terminological inconsistency, the lack of sufficiently large patient samples, and the use of a retrospective data have compromised the majority of studies of late-onset psychosis.

Several reasons underlie the current diagnostic confusion including historical differences in the approach to psychiatric nosology (e.g., Emil Kraepelin and Eugene Bleuler) that have persisted over time and continue to influence our current classification systems, different definitions and usage of the same term (e.g., the term late paraphrenia, has been used by some to denote a distinct disorder but by others as a means to describe schizophrenia with late-onset) and an overall lack of conceptual clarity (i.e., what is the relationship between early- and late-onset forms of psychosis). Terminological/diagnostic confusion and uncertainty have been able to continue festering, in part, because the cause, or underlying etiopathophysiological mechanisms, of psychosis in general and late-onset psychosis, in particular, are still unknown. This should not, however, hold-up the very important work of classification based upon an in-depth examination of the clinical nature of primary psychosis in older patients. Recently, an international group of experts argued for the abandonment of the once prevalent term, "late paraphrenia" (Howard et al., 2000). Their proposal of the terms "late-onset

schizophrenia" (if onset after 40 years old) and "very-late-onset schizophrenia-like psychosis" (if onset after 60 years old) were, however, problematic.

The diagnostic criteria associated with these proposed terms were not clearly outlined and this led to ongoing inconsistency and confusion about their meaning and how they were to be used (e.g., Rodriguez-Ferrera, Vassilas & Haque, 2004; Girard & Simard, 2008; Huang & Zhang, 2009; Vahia et al., 2010). Importantly, the authors of the international consensus statement (Howard et al., 2000) failed to address the fate of the current diagnostic category "delusional disorder" and what to do, diagnostically, with patients previously referred to as "late paraphrenia" who may not have met criteria for schizophrenia but may have met criteria for delusional disorder or who may not have met criteria for either (Quintal, Day-Cody & Levy, 1991; Almeida, Howard, Levy & David, 1995a). It still remains unclear whether there is any validity or usefulness to distinguishing schizophrenia and delusional disorder in the late-onset population with primary psychosis (Evans et al., 1996; Riecher-Rössler et al., 2003; Quintal et al., 1991). Given the typical absence of any thought disorganization, catatonia and negative symptoms in patients with late-onset non-affective psychosis (e.g., Pearlson et al., 1989; Howard, Castle, Wessely & Murray, 1993; Heaton et al., 1994, Jeste et al., 1995; Castle, Wessely, Howard & Murray, 1997; Rodriguez-Ferrera et al., 2004; Sato, Bottlender, Schroter & Moller, 2004), the diagnosis of schizophrenia over that of delusional disorder often comes to rest on the rather arbitrary and certainly subjective DSM-IV diagnostic criteria of whether the delusions are bizarre or not, and/or whether the hallucinations are

prominent or not. Furthermore, it has been cogently argued that late-onset psychosis should not be designated as schizophrenia at all (Almeida et al., 1995a; Andreasen, 1999; Taylor, 2001). Perhaps the most salient issue here is that schizophrenia beginning earlier in life, has been conceptualized as a developmental disorder (Rapoport, Addington, Frangou & Psych, 2005) and most conditions, which develop later, whether they be somatic or psychiatric, are viewed as degenerative.

With the changing demographic, and rapidly expanding growth of the segment of the population over the age of 60-65, there is almost certainly going to be an increase in the number of older individuals affected by new-onset psychosis (Jeste, 2000). Diagnostic clarification is, therefore, a timely imperative that has the potential to advance efforts to identify the pathobiological underpinnings of the condition, the course of illness and the most effective treatment. I have had the opportunity to characterize a large cohort of prospectively followed patients with first episode late-onset psychosis and to address the question of whether there is any validity to, or usefulness in, distinguishing between schizophrenia and delusional disorder in these patients. I will begin with an overview of the significant historical contributions, followed by a summary of what is currently known about the nature of late-onset psychosis and end with a discussion of the current issues facing its diagnosis. Given the diagnostic/terminological inconsistency and ambiguity associated with this presentation, for the sake of brevity and clarity, I will hereon refer to these patients as those with "late-onset psychotic disorder".

Historical contributions to late-onset psychotic disorder

The origins and development of the diagnostic concept of late-onset psychotic disorder is a complicated narrative involving contributions from a range of international researchers often working in isolation or in parallel, rather than in an integrative fashion (Riecher-Rössler, Rössler, Förstl, & Meise, 1995). The following is a review of the most significant historical contributions to the current diagnostic issues.

The literature on late-onset psychotic disorder dates back to over a century ago when Emil Kraepelin (Kraepelin, 1904; Kraepelin, 1919; Kraepelin, 1921), provided modern-day psychiatry with a highly comprehensive description and categorization of psychotic disorders that continues to influence today's practice (Jablensky, 2007; Kendler, 2009). Kraepelin (1919, 1921) proposed, albeit tentatively, that the non-affective primary psychotic disorders could be differentiated, on their phenomenology and different courses of illness, into three main groups: dementia praecox (now referred to as schizophrenia), paraphrenia, and paranoia (now referred to as delusional disorder). Although Kraepelin did not define or formally distinguish these groups by age of onset, he did remark that paraphrenia and paranoia were characterized by a relatively later age of onset than what was typical for dementia praecox. Whereas in his series of dementia praecox patients, the majority of the cases began between the fifteenth and thirtieth year, the majority of his paraphrenia and paranoia patients had onset after the age of 30 (Kraepelin, 1919; Kraepelin, 1921). However, a far from insignificant proportion of Kraepelin's dementia praecox patients (i.e., 10%) also had an onset over the age of 40.

Although Kraepelin believed that the "clinical forms of dementia praecox…are distinctly influenced by age" (1919, p. 209) with this advanced age of onset being characterized by the "paranoid" sub-type (i.e., predominated by symptoms of delusions and hallucinations), he also acknowledged his uncertainty about whether these late-onset cases should be regarded as dementia praecox at all. Separate from these three main psychotic disorders, Kraepelin (1904) also described a very small number of cases (i.e., 12 cases in 10 years) that he labeled as "presenile delusional insanity", a diagnosis that he specifically defined by its late age of onset. Following is a brief discussion of how Kraepelin proposed to differentiate these four groups of paranoid states.

Kraepelin defined the largest of these groups, dementia praecox, as "a series of states, the common characteristic of which is the peculiar destruction of the internal connections of the psychic personality" (1919, p. 3). The "psychic clinical picture" of dementia praecox was characterized by two principal disorders:

> 1) "a weakening of those emotional activities which permanently form the mainsprings of volition. In connection with this, mental activity and instinct for occupation become mute…The result…is emotional dullness, failure of mental activities, loss of mastery over volition, of endeavor, and the ability for independent action" and 2) "…the loss of the inner unity of the activities of intellects, emotion, and volition in themselves and among one another…This annihilation presents itself to us in the disorders of association, in incoherence of the train of thought, in the sharp change of moods as well as in desultoriness and derailments in practical work…The near connection between thinking and feeling, between deliberation and emotional activity on the one hand, and practical work on the other is more or less lost." (1919, p. 74-75).

In current practice, these symptoms would likely be referred to as the negative syndrome, thought disorganization and cognitive dysfunction (e.g., deficits in executive functioning) now accepted as key clinical aspects of schizophrenia (Zec, 1995; Andreasen, 1999). However, Kraepelin wrote that the paranoid sub-type, which characterized late-onset cases, did not have these symptoms to a particularly severe degree:

> "in definitely advanced age, the paranoid forms appear, which on the one hand lead not so very frequently to the most severe forms of psychic weakness, but on the other hand show very little tendency to essential improvement of the morbid state when it is once developed." (1919, p. 210).

In comparison, other forms of dementia praecox (e.g., catatonic, depressive), which were characteristic of earlier ages of onset, had more severe courses according to Kraepelin (1919).

Kraepelin defined the largest subtype of paraphrenia, paraphrenia systemica, as "extremely insidious development of a continuously progressive delusion of persecution, to which are added later ideas of exaltation without decay of the personality" (1919, p. 284). Kraepelin distinguished paraphrenia from dementia praecox on the basis that the negative, disorganized and cognitive symptoms, although present, were to a far lesser degree: "…because of the far slighter development of the disorders of emotion and volition, the inner harmony of the psychic is considerably less involved" (1919, p. 283). According to Kraepelin, "it is above everything the permanent preservation of the psychic personality that has caused me to delimit [paraphrenia] from the paranoid forms of

dementia praecox" (1919, p.299). Kraepelin acknowledged that such a differentiation might be called into doubt given that "in dementia praecox, especially the paranoid forms, the disintegration of the personality may not take place" (1919, p. 299). However, he felt that in such cases of dementia praecox, there remained an underlying "defect" and the potential that "a fresh outbreak of the disease may yet transform the hallucinatory or paranoid weak-mindedness into a drivelling, silly, negativistic or dull dementia" (1919, p. 299). It should be noted that Kraepelin eventually abandoned the diagnostic entity of paraphrenia in subsequent editions of his textbook (Riecher-Rössler et al., 1995), in large part due to the work of Mayer (1921). Mayer (1921) had conducted a file review of 78 patients that Kraepelin had personally diagnosed as paraphrenia, and reported that 30 of the cases eventually showed symptoms characteristic of dementia praecox (i.e., prominent thought disorder and personality deterioration). This included the re-classification of 8 of the 9 patients diagnosed with the most severe form of paraphrenia, paraphrenia phantastica, as dementia praecox (Mayer, 1921) – a position that Kraepelin himself was seemingly in agreement with when he wrote "it is wholly impossible to delimit them sharply in any way" (Kraepelin, 1919, p. 253). Another twenty cases were re-diagnosed as having other disorders including paranoia, organic dementia and manic-depressive illness (Mayer, 1921). However, the remaining third of cases had a course that remained stable although Mayer wrote that he suspected they too would eventually turn out to have dementia praecox with time. No differences in the initial clinical pictures could predict the various outcomes (Mayer, 1921). Despite these findings, Mayer (1921) recognized that disorders of volition were not as prominent in patients originally described by

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Kraepelin as paraphrenic compared to those with dementia praecox. Interestingly enough, he suggested this might be due to their relatively later age of onset because the cognitive processes would be already well established by the time psychosis appeared (Mayer, 1921).

The diagnosis of paranoia was defined by Kraepelin as the "insidious development of a permanent and unshakable delusional system resulting from internal causes, which is accompanied by perfect preservation of clear and orderly thinking, willing, and acting" (1921, p. 212). Compared to schizophrenia, Kraepelin observed that "the conduct is invariably far more grounded on deliberation or emotional processes than the impulsive peculiarities of the schizophrenic" and "the whole personality, in spite of its morbid features, appears more comprehensible" (1921, p. 273). In other words, the paranoid patient had an absence of the disorganized behaviour, thoughts and affect that characterized schizophrenia. The distinction between paraphrenia and paranoia was much more difficult to justify, especially "in the first periods of the malady" (Kraepelin, 1921, p. 274). Fundamentally, Kraepelin (1921) felt that the course of illness for the paranoid patient was relatively more mild and one that typically avoided institution in comparison to the paraphrenic patient.

Kraepelin (1904) also described a group of late-onset psychosis patients (i.e., at age 50 in males, between the ages of 55 and 65 in females) who he diagnosed as having "presenile delusional insanity". This presentation was characterized by "gradual

development of marked impairment of judgment, accompanied by numerous

unsystematized delusions of suspicion and greatly increased emotional irritability"

(Kraepelin, 1904, p. 364). Kraepelin (1904) acknowledged that many would consider

these cases to be dementia praecox. However, he felt that they could be differentiated

from dementia praecox based on their lack of catatonic symptoms and apathy, and by

their predominant disturbance being in judgement (reflected by "the retention of the most

fantastic delusions" (p. 366)) and not in emotions or actions. What is unclear is whether

Kraepelin specifically compared his late-onset dementia praecox patients to those he

labeled as "presenile delusional insanity". Similarly to his last-onset dementia praecox

cases, there was a predominance of women in his "presenile delusional insanity" group.

In terms of prognosis, this group did not progress to "profound dementia or confusion of

speech but by a moderate deterioration with isolated, changeable and incoherent

delusions" (Kraepelin, 1904, p. 368).

Although Kraepelin largely emphasized differences in the course of illness in his

distinction of these disorders, he also differentiated the paranoid subtype of dementia

praecox, paraphrenia, paranoia and presenile delusional insanity in terms of the nature of

their positive symptoms (Kraepelin, 1904; Kraepelin, 1919; Kraepelin, 1921). The

presence of delusions was common across disorders, however, 'paranoia' as a diagnostic

entity, was said to be associated with delusions that were non-bizarre and well-

systematized (i.e., united by a single theme, organized and unchanging). This was in

contrast to dementia praecox and paraphrenia, which were typically characterized by

bizarre, more poorly systematized delusions. Although the delusions of presenile

delusional insanity were described as non-bizarre in nature, Kraepelin believed that the

group could be differentiated from paranoia on the basis of the presence of non-

systematized delusions (1904). The groups, as described by Kraepelin, also appear to

differ in terms of hallucinations. In the paranoid form of dementia praecox and

paraphrenia, hallucinations are common, conspicuous and can be of a number of

modalities (Kraepelin, 1919). In presenile delusional insanity, hallucinations were present

in only a few of the cases and were described as auditory in nature. In contrast to these

three groups, Kraepelin asserted that "genuine hallucinations do not occur" in paranoia

(Kraepelin, 1921, p.215). However, his own descriptions seemed to contradict this when

he wrote that his paranoid patients actually had "visionary experiences" such as seeing

"stars, shining figures and divine apparitions", and that some patients were in "constant

communication with God" experienced as the "emergence of exhorting, warning, assuring

thoughts, which in the manner of the 'voice of conscience' are traced back to

supersensual influences" (1921, p.215-6). The issue of whether hallucinations ought to be

permitted, and if so, to what extent, under the diagnosis of delusional disorder has

become a topic of ongoing debate (Kendler & Tsuang, 1981).

In summary, Kraepelin's work on (late-onset) psychotic disorders demonstrated

that an increasing age at the time of onset was associated with an over-representation of

the female sex and a predominance of delusions and/or hallucinations, and not the

catatonia, thought disorganization and negative symptoms, which characterized early-

onset illness. Kraepelin's phenomenological descriptions and his approach to the

categorization of these late-onset paranoid disorders, despite its relative arbitrariness and

his own hesitancy in doing so, have been profoundly influential. Kraepelin's struggle to

understand the relationship between early and late-onset psychotic illness remains an

issue of ongoing debate today:

> "The decision as to which morbid disorders of the age of involution are to
> be reckoned with dementia praecox and which are to be regarded as
> psychoses of another kind, will therefore always depend on the question,
> how far the differences in the form of the clinical phenomena are
> conditioned by the character of the morbid process and how far by the
> changes of advancing age in the personality." (Kraepelin, 1919, p. 230).

The next major contribution was the work of Eugene Bleuler, best known for

changing the Kraepelian term, "dementia praecox", to schizophrenia and by defining the

"fundamental" symptoms of schizophrenia to be affective flattening, associative

loosening, ambivalence and autism (Bleuler, 1950). In contrast to Kraepelin, who used

the course of illness as the main criterion to determine psychiatric nosology, Bleuler

focused on cross-sectional symptomatology and underlying psychological mechanisms to

define schizophrenia (1950). This approach, given the common occurrence of delusional

formation, led Bleuler (1924; 1950) to broaden of the boundaries of paranoid

schizophrenia to include Kraepelin's groups of paraphrenia, presenile delusional insanity

and many cases of paranoia (Kendler & Tsuang, 1981). The Bleulerian concept of

schizophrenia was highly influential, and was adopted by the early editions of the DSM

(Kendler & Tsuang, 1981). In the footsteps of his father, Manfred Bleuler, continued the

study of psychotic disorders with special attention to late-onset cases. The younger

Bleuler (1943) treated and followed 126 chronically hospitalized patients with a late-

onset schizophrenia-like illness. He proposed the diagnostic term "late-onset

schizophrenia" for these patients, who by definition had developed psychosis after the age

of 40, had symptomatology that did not differ fundamentally from that of schizophrenia

in early life and who did not have an amnestic syndrome or accompanying physical

findings unequivocally indicating that the illness could be due to brain disease (Bleuler,

1943). Bleuler found that this group corresponded to 15% of all schizophrenic patients,

with two-third of cases having onset between ages 40 and 50 and 4% with onset over age

60 (1943). Although by definition the clinical presentation of late schizophrenia could

not be fundamentally different from early-onset schizophrenia, Bleuler would note that

they tended to have less affective flattening and better outcomes (1943). Furthermore,

half of his late-onset patients had a "special kind of schizophrenic coloring" including a

paraphrenia-like presentation (Bleuler, 1943). Bleuler's notion that primary psychosis

beginning in later life was essentially the same schizophrenic illness that afflicted

younger people would significantly influence German psychiatry over the second half of

the 21st century (Riecher-Rössler et al., 1995).

In the mid 1950s, psychiatric researchers in the United Kingdom began to pay

greater attention to late-onset psychotic disorder. Roth and Morrissey (1952) published a

retrospective review of 150 case records of all patients admitted to a psychiatric facility

over the age of 60 and indentified 12 patients who presented with late-onset psychotic

disorder. They were all noted to have delusions that developed "in the setting of a well-preserved intellect and personality, were often 'primary' in character, and were usually associated with the passivity failings or other volitional disturbances and hallucinations in clear consciousness, pathognomonic of schizophrenia" (Roth & Morrissey, 1952). Based upon these preliminary findings, Roth proposed a classification system of mental disorder in old age that included a separate category, which he labeled as "late paraphrenia", for patients presenting with "a well-organized system of paranoid delusions with or without auditory hallucinations existing in the setting of a well-preserved personality and affective response" (Roth, 1955). Of the cases meeting the proposed criteria, all but one had onset of symptoms after age of 45 with a majority (75%) having onset over age 60 (Roth, 1955). Using both retrospective and prospective data, Roth concluded that this group was distinct not only in clinical presentation, but also in outcome (defined in terms of being discharged, hospitalized or dead at 6 months and 2 years) from "senile psychosis" and "arteriosclerotic psychosis" (known as Alzheimer's dementia and vascular dementia in current nomenclature) with the late paraphrenia group having significantly less mortality at both time points. With respect to the differentiation from late life affective disorder, Roth claimed that "marked differences in course and outcome as well as clinical picture" make it "evident that the two disorders are largely independent", although stated that their differentiation was "not a problem peculiar to old age mental disorder and was not the subject of one of our hypotheses" (1955). However, it appears from the outcome data that a greater percentage of affective disorder patients, were discharged, compared to those with "late paraphrenia" who continued on as inpatients at 6

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months and 2 years post-admission (Roth, 1955). In Roth's (1955) opinion, the term "late

paraphrenia" best designated this group of late-onset psychotic disordered patients

because 1) for the great majority, the illness began after the age of 60 and 2) the

phenomenology and course of illness was similar to the paraphrenia psychotic disorder

originally described by Kraepelin. Notably, Roth's assertion that the majority of late

paraphrenia patients presented after the age of 60 is of dubious significance given that his

study included *only* patients aged 60 and above (Riecher-Rössler et al., 1995).

Regardless, onset after age 60 became a "quasi-obligatory diagnostic criterion" for late

paraphrenia (Riecher-Rössler et al., 1995). Furthermore, Roth's decision to reference

Kraepelin's "paraphrenia" group was criticized (Fish, 1960) based on (i) the belief that

Mayer (1921) could not show that paraphrenia was indistinguishable from dementia

praecox and (ii) that late paraphrenia could be confused with Bleuler's late-onset

schizophrenia. It appears that in response to these criticisms, Kay and Roth (1961)

clarified that late paraphrenia was "a suitable *descriptive* term, without prejudice as to

aetiology, for all cases with paranoid symptom-complex in which signs of organic

dementia or sustained confusion were absent, and in which the condition was judged from

the content of the delusional and hallucinatory symptoms not to be due to primary

affective disorder" (my italics). Furthermore, in keeping with the Bleulerian tradition,

Kay and Roth (1961) concluded that "if the kinship of a group of cases with the

schizophrenias must be decided, as we believe, by the presence or absence of the primary

or process symptoms of schizophrenia, the main group of the paraphrenic cases we have

studied, with their ideas of influence, primary delusions, hallucinations in clear

consciousness and oddities and at times incongruity of affect, must be regarded as schizophrenic" (1961). Although, Kay and Roth (1961) maintained that late paraphrenia was fundamentally a form of schizophrenia, the term "late paraphrenia" was adopted by the International Classification of Diseases as a diagnosis unto itself, and was employed as such by British psychiatrists – leading to a lack of conceptual clarity and ongoing debate surrounding the term's use in conjunction with that of Bleuler's "late-onset schizophrenia" (Riecher-Rössler et al., 1995). This, of course, ultimately made the clinical study of the disorder(s) very difficult.

Despite these criticisms and issues, Kay and Roth's (1961) case series of 99 late paraphrenia patients became the first highly detailed account of the clinical and pre-morbid features of late-onset psychotic disorder and was widely accepted. This included a "remarkably uniform" clinical picture characterized by "disorders of thought, mood and volition, by relatively good preservation of formal intellect, personality and memory, and by conspicuous hallucinations" (Kay & Roth, 1961). Kay and Roth (1961) also described the following typical demographic and pre-morbid features that seemed to characterize this group: female sex, social isolation, sensory deprivation (e.g., deafness, visual impairment), abnormalities of personality (e.g., "paranoid-schizoid" type) and a "somewhat increased" morbid risk of schizophrenia in first-degree relatives. The majority of these characteristics have since been consistently noted by other researchers (to be discussed at a later point in greater detail) and together suggested "syndromic coherence" (Howard & Rabins, 1997).

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In comparison to the early contributions of European researchers, there was a notable lack of research in late-onset psychotic disorders in North America until the 1980s. Harris and Jeste (1988) suggested that this may have been due to (i) the inconsistencies in terminology and classification, (ii) an overriding tendency to attribute late-onset psychosis to affective disturbances, general medical conditions or substances, or (iii) a lack of consensus regarding minimal age of onset and (iv) the difficulty following these patients long-term because of their primary problem of paranoia and sensory deficits as well as the high rates of mortality.

Unfortunately, the establishment of formal psychiatric diagnostic classification systems, namely, the Diagnostic and Statistical Manual of Mental Disorders (DSM) first published by the American Psychiatric Association (APA) in 1952, and the first revision of the International Statistical Classification of Diseases and Related Health Problems to include mental disorders published by the World Health Organization (WHO) in 1948 (ICD-6), did not resolve the terminological issue with respect to late-onset psychotic disorder. Indeed, ongoing change to the two classification systems over the last fifty years has only perpetuated the confusion.[1]

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[1] The discussion of the history of the nosological criteria for late-onset psychotic disorder has been limited the Diagnostic Statistical Manual of Manual Disorders and the eighth and subsequent editions of the International Classification of Disease, although the author recognizes that both European and American criteria for late-onset psychotic disorder pre-dates these manuals. For a review of these earlier criteria, please refer to Kendler and Tsuang (1981).

History of Late-onset Psychotic Disorder in the Diagnostic and Statistical Manual of

Mental Disorders (DSM)

The first edition of the DSM (APA, 1952) included the category of "involutional psychotic reaction", a form of psychosis occurring in mid to late life. It appeared to be a combination of Kraepelin's "presenile delusional insanity" and "involutional melancholia" (Munro, 1999). The main diagnostic features included symptoms of anxiety, insomnia, agitation, and delusions with a history of "compulsive personality type", but an absence of "previous history of manic depressive reaction" (APA, 1952, p. 24). The course was prolonged and could either be characterized "chiefly by depression" or "chiefly by paranoid ideas" (APA, 1952, p. 24). Notably, differentiation from other psychotic disorders (e.g., schizophrenic) in mid to late life was considered to be difficult (APA, 1952). Despite this, the DSM-I stated that other psychotic disorders (e.g., schizophrenic, affective) would "not be included in this category merely because of their occurrence in this age group" APA, 1952, p. 24). Clearly, the DSM-I recognized that a psychotic disorder could present for the first time in mid to late life, but there was a lack of consensus as to whether sub-groups existed within this age category. The second edition of the DSM (APA, 1968) included the somewhat more narrow diagnosis of "Involutional paranoid state (Involutional paraphrenia)" classified under the heading of "Paranoid States" in which delusions were an essential abnormality although "disturbances in mood, behavior and thinking (including hallucinations)" could be "derived from this delusion." The involutional paranoid state was described as a "paranoid psychosis…characterized by delusion formation with onset in the involutional

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period". Formerly it had been classified as the paranoid variety of involutional psychotic reaction (APA, 1968) and was felt to be a return to Kraepelin's original description of "presenile delusional insanity" (Munro, 1999). The diagnosis was to be distinguished from schizophrenia based on its "absence of conspicuous thought disorders typical of schizophrenia" (APA, 1968). The diagnosis of schizophrenia, also did not have an associated age limit. However, in DSM-III (APA, 1980), the diagnostic category, "involutional paranoid state/paraphrenia", was removed and a diagnosis of schizophrenia could not be made if symptom onset was after age 45. This decision appeared to be arbitrary in nature (Harris & Jeste, 1988). Be that as it may, at this point, a chronic psychotic illness occurring after age 45 was to be classified as an "atypical psychosis". In a rebuttal, Rabins, Parker and Thomas (1984) published an article, "Can schizophrenia begin after age 44?". They described 35 patients who met Roth's original definition of late paraphrenia with onset after 44 years old, 32 of whom also fulfilled DSM-III criteria for either schizophrenia or schizophreniform disorder, with exception of the age cut-off. The remaining 3 patients met criteria for paranoia (Rabins et al., 1984). Consequently, in the revised edition of the DSM-III (APA, 1987), the diagnosis of schizophrenia could be made if the onset was over the age of 45, noted with the specifier, "late onset". The DSM-IV (APA, 1994) subsequently removed the "late onset" specifier for schizophrenia. Therefore, according to the DSM-IV, all patients who meet criteria for schizophrenia were to be diagnosed as such, regardless of age of onset. This was consistent with the manual's emphasis upon phenomenology as well as its assiduous avoidance of etiological terms and overrode the emerging findings that compared to early-onset cases, late-onset

was characterized by female preponderance, better marital and employment histories, more paranoid delusions and greater range of hallucination modalities, less disorganization and fewer negative symptoms (APA, 1994).

The other non-affective psychotic disorder, contained within the DSM, namely, delusional disorder or paranoia (pre-DSM-IIIR), was never associated with a particular age cut-off or specifier. The closest that the DSM came to mentioning a later-onset in delusional disorder was in the DSM-III-R (APA, 1987), which stated that "the average age of onset has been found to be between 40 and 55." However, in the most recent edition, it is reported that the "age of onset of Delusional Disorder is variable, ranging from adolescence to late in life" (APA, 2000).

History of Late-onset Psychotic Disorder in the International Classification of Diseases

(ICD)

The ICD took a different path with regard to the diagnosis of late-onset psychotic disorder, which closely mirrored the British discussion on the subject (Riecher-Rössler et al., 1995). The eighth revision of the International Classification of Diseases (ICD-8) (WHO, 1967) included under the category of "other paranoid states", the diagnosis of "paraphrenia (late)". The schizophrenia section did not include an age of onset limit. The next revision, ICD-9 (WHO, 1978), included a distinct codeable diagnosis for paraphrenia, within the larger category of "delusional disorders". However, rather confusingly, but in keeping with Kay and Roth's (1961) conceptualization, the ICD-9

defined paraphrenia as "a form of *schizophrenia* characterized by delusions (of

persecution or grandeur or jealousy); symptoms may include anger and anxiety and

aloofness and doubts about gender identity; unlike other types of schizophrenia the

patients are usually presentable and (if delusions are not acted on) may function in an

apparently normal manner" (my italics; WHO, 1978). Furthermore, the ICD-9 described

the clinical picture of paraphrenia as being dominated by conspicuous hallucinations and

an absence of affective symptoms and thought disorder , consistent with Kay and Roth's

description (1961). Although the diagnosis did not have an explicit age cut-off, it was

somewhat implied by the inclusion of the terms involutional paranoid state, late

paraphrenia and paraphrenia (involutional) as part of the paraphrenia diagnosis. Given the

ongoing ambiguity and conflict surrounding both the term and its concept (e.g., its

relationship with schizophrenia), early drafts of the ICD-10 did not include any mention

of paraphrenia or late paraprehenia, an omission that was swiftly challenged (Almeida,

Howard, Forstl & Levy, 1992). Almeida et al. (1992) felt that it was an inadequate

response to the increasing amount of evidence suggesting that the underlying etiological

processes of late paraphrenia may be different from that of schizophrenia and other

delusional disorders with early-onset. Ultimately, the ICD-10 (WHO, 1992) up to its most

recent version (WHO, 2007) included "paraphrenia (late)", but only as a term (not as a

diagnosis per se) under the diagnosis of delusional disorder. The placement of late

paraphrenia under the diagnosis of delusional disorder, however, generated internal

inconsistency. Almeida (1998) commented that it was "inappropriate because most

people with late paraphrenia display symptoms such as prominent hallucinations"

(Almeida, 1998) and these could technically not be present for a diagnosis of delusional disorder to be made. The ICD-10's (WHO, 2007) attempt to provide some flexibility on this issue by allowing "occasional or transitory auditory hallucinations, particularly in elderly patients…provided that they are not typically schizophrenic and form only a small part of the overall clinical picture" only gave way to more confusion by essentially blurring the distinction between the diagnoses of schizophrenia and delusional disorder in the re-classification of late paraphrenia patients (Howard & Rabins, 1997). Furthermore, using ICD-10 criteria, the majority (approximately two-thirds) of patients previously diagnosed with late paraphrenia could be classified under the diagnosis of paranoid schizophrenia instead of delusional disorder (Quintal et al., 1991; Howard, Almeida & Levy, 1994a). In terms of the ICD-10 diagnosis of delusional disorder, no age limit was provided although it is noted that the onset of delusional disorder is "commonly in middle age" (WHO, 1992). Finally, of note, the ICD-10 specifically excludes the term "involutional paranoid state" from the diagnosis of paranoid schizophrenia, which does not formally contain age of onset criteria. The term "involutional paranoid state" was instead included under the diagnosis of "other persistent delusional disorders" (WHO, 1992).

Characteristics of Late-Onset Psychotic Disorder

In spite of the variations and inconsistencies in terminology, diagnostic criteria and age cut-offs, all of which could influence which patients are, or have been, included in any particular research study, a remarkable consensus has emerged for many of the

features of late-onset psychotic disorder, starting with Kraepelin's description over 100 years ago. In the discussion of the characteristics below, the term employed by the primary authors to designate diagnosis has been maintained, with the exception of when groups of studies with a range of diagnoses (e.g., late paraphrenia, schizophrenia, delusional disorder) are summarized together. In these instances, the term "late-onset psychotic disorder" has been applied for the sake of brevity.

Incidence and prevalence

In 1988, Harris and Jeste carried out a review of the available literature and calculated that of all patients meeting diagnostic criteria for schizophrenia, 13% had their illness onset in the 5th decade, 7% percent had an illness onset in the 6th decade and for 3%, their illness began in or after the 7th. A more recent study found similar proportions of patients with schizophrenia or paranoid psychosis, in each age category, after the age of 40 (Riecher-Rössler, Löffler & Munk-Jørgensen, 1997). Using a large inner-city, catchmented area of London (United Kingdom) and defining their sample as those with their first contact with psychiatric services, Castle and Murray (1993) determined an approximate incidence of 12.6 per 100,000 population per year for those over age 45 who met DSM-IIIR criteria for schizophrenia. Notably, this was half the rate of that seen in the 16 to 25 year old group (Castle & Murray, 1993). It is not surprising that a higher incidence rate of 26 per 100,000 was reported from the same catchment area when the diagnostic criteria of "late paraphrenia" as defined by Roth (1955) (Holden, 1987), were used, given that this category would 'capture' patients meeting criteria for both delusional

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disorder and schizophrenia. A case registry review of a geriatric psychiatry inpatient unit, from 1993 to 2002, determined that 3.3% of all admissions, with DSM-IV defined schizophrenia, had an onset of illness after age 40 (Alici-Evcimen, Ertan & Eker, 2003). In a recent study, Ostling, Pálsson and Skoog (2007) found that 8% of all non-demented 70-year-olds, in a Swedish population, developed first-onset, primary, non-transient psychotic symptoms (delusions, hallucinations or paranoid ideation in the absence of delirium or drug effects) during a 20-year follow-up period. Although, the use of different diagnostic labels and criteria in late-onset psychotic disorder has made the interpretation of epidemiological findings challenging, these studies clearly demonstrate that late-onset psychotic disorder is common.

Gender

Kraepelin first observed that, while there is a slight male predominance (57.4%) in dementia praecox patients (referred to as schizophrenia in current nomenclature) overall, "after the fortieth year, women predominate" (Kraepelin, 1919, p. 231). This over-representation of females in the late-onset psychotic disorder group, regardless of the term or diagnostic criteria used, remains one of the most consistent and replicable findings (e.g., Kraepelin, 1904; Bleuler, 1943; Kay & Roth, 1961; Rabins et al., 1984; Holden, 1987; Pearlson et al., 1989; Castle & Murrary, 1993; Häfner, Riecher-Rössler, An Der Heiden, Maurer, Fätkenheuer & Löffler, 1993; Howard et al., 1994a; Castle et al., 1997; Jeste et al., 1997; Riecher-Rössler et al., 1997; Hassett, 1999; Rodriguez-Ferrera et al., 2004; Romero-Rubiales, Reeves & Howard, 2004; Vahia et al., 2010; Bogren,

Mattisson, Isberg, Munk-Jørgensen & Nettelbladt, 2010). While a recent systematic

review of community-based cohorts reported from the pooled odd ratios of six studies

that female gender was *not* significantly associated with onset of psychoses over the age

of 40 (Brunelle, Cole & Elie, 2011), the methodological approach used had serious

limitations. These include the inclusion of studies with patients who had a prior history

of psychotic symptoms, affective disorders and cognitive symptoms, including dementia,

and the inclusion of studies with the non-specific outcome of psychotic symptoms rather

than an actual primary psychotic disorder. In fact, the one cohort study included in this

pooled analysis that specifically looked at patients at risk for first-episode late-onset

schizophrenia and other non-affective psychotic disorders over a 50 year period did find a

female preponderance in these cases (Bogren et al., 2010). Based upon an extant review

of studies, which included patients from a number of cultural backgrounds and a variety

of health service models, Castle (1999) concluded that potential social confounders such

as differences in role-expectations, help-seeking behaviours, marital status and premorbid

adjustment between the genders could not fully explain the finding of female

preponderance in late life. One possible explanation is the protective role of estrogen and

how its withdrawal in mid-life creates the milieu for late-onset psychotic disorder to

develop (Seeman, 1999). The over-representation of females in late-onset psychotic

disorder is an important finding and may hold information about the differences between

the sexes, in terms of how the brain ages, as suggested by Castle (1999).

Pre-morbid personality and functioning

Late-onset psychotic disorder has also been consistently associated with higher pre-morbid functioning with respect to their occupational, social and marital histories, compared to early-onset psychotic disorders (Castle et al., 1997; Jeste et al., 1997; Brodaty, Sachdev, Rose, Rylands & Prenter, 1999; Vahia et al., 2010). Patients with late-onset psychotic disorder have been found to have more pre-morbid schizoid or paranoid personality traits compared to those with late-life affective disorder (Kay & Roth, 1961) and healthy controls (Pearlson et al., 1989; Brodaty et al., 1999). However, it is unclear how they compare to early-onset schizophrenia patients in this regard with one chart review reporting higher percentage of premorbid schizoid traits in late-onset patients (Pearlson et al., 1989) whereas another study employing a subject- and informant-informed scale of premorbid personality detected no difference in such traits as being odd, eccentric, suspicious and detached (Brodaty et al., 1999).

Family history

Patients with late-onset psychotic disorder have been reported to be less likely to have a family history of schizophrenia compared to individuals with early-onset schizophrenia (Kay, 1972; Pearlson et al., 1989; Castle et al., 1997; Brodaty et al., 1999). In late paraphrenia patients with onset over 55, the risk of a family history of schizophrenic illness was found to be no more likely than in healthy controls (Almeida, Howard, Levy & David, 1995b; Howard et al., 1997). It must be emphasized, however, that ascertainment of family history in older patients may be more difficult than in those who are younger for a number of reasons such as generational differences in the level of

knowledge of psychiatric illness/diagnosis in family members and differences in the intensity of the stigma of mental illness which can influence reportage.

Sensory deficits

Historically, it has been thought that sensory deficits, both visual and auditory, are strongly associated with the development of late-onset psychotic disorder and may constitute a risk factor (Kay & Roth, 1961; Post, 1966). However, the results of more recent research have not been as clear. Prager and Jeste (1993) reported that late-onset schizophrenia patients were comparable to age-matched early-onset schizophrenia patients, mood disorder patients and healthy controls, on tests of auditory and visual function, although all patient groups were found to be more impaired than healthy controls when tested using their corrective measures (e.g., the patient's personal eye glasses or hearing aids). The latter observation suggests suboptimal correction of sensory impairments in older psychiatric patients (Prager & Jeste, 1993). In contrast, Brodaty et al. (1999) reported that late-onset schizophrenia patients had more severe corrected hearing impairment (based on self/informant report and interviewer observation) compared to early-onset schizophrenia patients, but were comparable to age-matched healthy controls. Notably the old early-onset schizophrenia was statistically significant younger than the other groups. There was no difference in corrected visual impairment between the three groups (Brodaty et al., 1999). Similarly, Pearlson et al. (1989) reported, based on a chart review, that the late-onset schizophrenia group had significantly more hearing impairment compared to the age-matched early-onset schizophrenia group and

that they were comparable on visual deficits. The discrepancy in hearing deficit findings

between these studies and the Prager and Jeste study (1993) could be due to the

differences between the two studies in the mode of assessment of sensory impairments

(e.g., tests versus report/crude observation). Still, a systematic review of community

cohort studies found that visual impairment, but not hearing impairment, was a risk factor

for the development of psychosis or psychotic disorder in late life (Brunelle et al., 2010).

However, the patient samples of the studies included in this systematic review appear to

include a much broader group of patients with psychosis as previously mentioned.

Social isolation, immigration and negative life events

Evidence suggests that patients with late-onset psychotic disorder are more

socially isolated compared to age-matched healthy controls (Almeida et al., 1995b;

Brodaty et al., 1999), patients with late-life affective disorder or organic psychoses (Kay

& Roth, 1961) and possibly older patients with early-onset schizophrenia if defined on the

basis that the patient is living alone or not (Pearlson et al., 1989) or by the number of

friends they have (Brodaty et al., 1999). However, no difference was detected between

late-onset and old early-onset schizophrenia patients on a subject- and informant-

informed scale of social isolation (Brodaty et al., 1999). Recent studies have shown that

certain immigrant populations may be at greater risk of developing late-onset psychotic

disorder after the age of 60 compared to non-immigrants (Reeves, Sauer, Stewart,

Granger & Howard, 2001; Mitter, Krishnan, Bell, Stewart & Howard, 2004). This was

thought to be possibly due to the relative social isolation of immigrants (Reeves et al.,

2001), but a follow-up study from the same group in the United Kingdom found no difference between the migrant and British-born groups with "very-late-onset schizophrenia-like psychosis" in terms of the proportion that were living alone, never married or childless (Mitter et al., 2005). Another possible psychosocial explanation is that the stressful experiences that led to the individual immigrating in the first place or associated with immigration in and of itself can interact with a patient's innate vulnerability and lead to the onset of psychosis (Mitter et al., 2005; Morgan, Charalambides, Hutchinson & Murray, 2010). For example, a retrospective chart review of child holocaust survivors, that involved diagnostic reclassification according to current nosology, found a significant association between the severity of persecution (e.g., detained in a concentration camp and loss both parents) endured during the holocaust and the development of late-onset schizophrenia (Reulbach, Bleich, Biermann, Pfahlberg & Sperling, 2007). However, the very high degree of co-morbid post-traumatic stress disorder and depression in this sample makes it difficult to interpret the significance of this finding for the population of patients with primary late-onset psychosis. Systematic study of other psychosocial stressors that might be specific to the development of a primary psychosis in late life (e.g., recrudescence of earlier trauma, the greater likelihood of loss bereavement as one ages, financial difficulties, retirement) has yet to be carried out (Howard et al., 2000).

Phenomenology

Recent studies of late-onset psychotic disorder have consistently supported Kraepelin's original observation (1904) of a relative absence of formal thought disorder with rates ranging from 1.4% (Castle et al, 1997) to 26.9% (Brodaty et al., 1999), which are significantly less when compared to rates associated with early-onset illness (Pearlson et al., 1989; Howard et al., 1993; Almeida et al., 1995a; Castle et al., 1997; Brodaty et al., 1999). There is one reported exception based upon a sample of chronically hospitalized patients (Huang & Zhang, 2009), which arguably represents a small minority of patients and which may be, in part, secondary to the effects of institutionalization. Affective blunting or flattening, long thought to characterize schizophrenia (Bleuler, 1950) and to be absent from in late-onset patients (Kraepelin, 1904; Bleuler, 1943; Kay & Roth, 1961) has been consistently found to a lesser degree in patients with late-onset psychotic disorder compared to their earlier-onset counterparts (Pearlson et al., 1989; Howard et al., 1993; Jeste et al., 1995; Castle et al., 1997; Sato et al., 2004), with one exception (Brodaty et. al, 1999) in which no difference was detected. Notably, the absolute prevalence of affective blunting in this latter study was considerably higher (i.e., 33%) compared to the proportion of patients reported by the other studies (i.e., 0% to 7.4%). Late-onset patients have been also been associated with a significantly lower score on the negative symptoms of alogia/mutism (Sato et al., 2004) and avolition/apathy (Jeste et al., 1995), although not consistently (Brodaty et al., 1999). The overall severity of negative symptoms on validated scales (e.g., The Scale for the Assessment of Negative Symptoms (SANS)) has been reported to be less in late-onset patients compared to old patients with early-onset illness (Brodaty et al., 1999; Rodriguez-Ferrera et al., 2004), however, others

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have not detected a difference (Huang & Zhang, 2009; Vahia et al., 2010). Notably, both late-onset schizophrenia patients and age-matched early-onset schizophrenia patients had significantly lower global scores of negative symptoms compared to young schizophrenic patients (Heaton et al., 1994).

Reports about the prevalence of patients with catatonia has been somewhat mixed with both lower (2.2% versus 8%) (Howard et al., 1993) and similar (5.6% versus 4.5%) (Pearlson et al., 1989) percentages being observed between late-onset and age-matched early-onset psychotic disorder groups, although the latter study, consisting of a smaller sample size, may have been under-powered to assess for differences in catatonia due to its relative infrequency overall. Notably, when a group of non-affective psychotic patients with onset over 60 years old is compared to a non-affective psychotic group with onset before 25 years old, the difference in the percentage of patients with catatonia at the time of presentation is quite striking (0% versus 12%, respectively) (Castle et al., 1997).

The presence of partition delusions, which is the belief that people, animals, materials or radiation can pass through a structure that would normally constitute a barrier to such passage (Pearlson et al., 1989; Howard, Castle, O'Brien, Almeida & Levy, 1992) and persecutory delusions (Pearlson et al., 1989; Howard et al., 1993; Sato et al., 2004) appear to be quite characteristic of late-onset psychotic disorder. Auditory hallucinations are also highly prevalent in late-onset psychotic disorder patients (as reviewed by Almeida et al., 1995a), and some have suggested that third person and abusive auditory

hallucinations are reported more often in late-onset than young early-onset patients (Howard et al., 1993; Castle et al., 1997). Howard et al. (2000) suggested that late-onset schizophrenia patients are more likely to report a wider range of perceptual misperceptions or hallucinations compared to their early-onset counterparts, although this difference has not been consistently reported (Brodaty et al., 1999). In keeping with Kraepelin's (1919) original observation, it has been thought that the paranoid subtype of schizophrenia is more likely to characterize late-onset compared to age-matched early-onset schizophrenia patients (Jeste et al., 1995), although, in a recent publication from the same research group, with a larger sample, no such difference was detected (Vahia et al., 2010). Overall severity of positive symptoms is thought to be less in late-onset patients compared to age-matched early-onset patients (Vahia et al., 2010), although previous, albeit smaller, studies found no difference in this respect (Jeste et al., 1995; Brodaty et al., 1999; Huang & Zhang, 2009). No differences have been reported in the presence or severity of depressive symptoms between late-onset and age-matched (Rodriguez-Ferrera et al., 2004; Vahia et al., 2010) or young (Riecher-Rössler et al., 1997; Sato et al., 2004) early-onset psychotic disorder patients.

Everyday functioning and quality of life

On the Instrumental Activities of Daily Living (IADLs), Brodaty et al. (1999) reported less impairment in the late-onset schizophrenia patients compared to old early-onset schizophrenia patients. On more in-depth measures of daily functioning and health-related quality of life, Vahia et al. (2010) found that patients with late-onset schizophrenia

were better off than elderly patients with early-onset schizophrenia, even when they included duration of illness as a co-variant. Not surprisingly, both patient groups were significantly worse off on these functioning measures when compared to age-matched controls (Brodaty et al., 1999; Vahia et al., 2010).

Cognitive performance

Both late-onset and early-onset psychotic disorder patients have consistently been found to do more poorly on most tests of cognitive performance compared to age-matched healthy controls (Miller, Lesser, Boone, Hill, Mehringer & Wong, 1991; Jeste et al., 1995; Almeida, Howard, Levy, David, Morris & Sahakian, 1995c; Sachdev, Brodaty, Rose & Cathcart, 1999; Vahia et al., 2010). A recent meta-analysis examining the relationship between age at onset and cognition in schizophrenia reported that late-onset patients (based on effect sizes compared to healthy controls) had a pattern of relatively greater impairment on tests of auditory and visual attention, fluency and visuospatial construction than on tests of arithmetic, digit symbol coding, verbal memory and vocabulary (Rajji, Ismail & Mulsant, 2009). This pattern of neurocognitive deficits was essentially the opposite of the pattern seen in patients with youth-onset (before age 20) and those with first-episode early-onset (between 20 to 39 years old) schizophrenia (Rajji et al., 2009). Post-hoc comparisons between groups found that individuals with youth-onset schizophrenia were more impaired on arithmetic, digit symbol coding, vocabulary and Wisconsin card sorting and similar tests, but less impaired on auditory and visual attention compared to those with late-onset schizophrenia (Rajji et al., 2009). Similarly,

individuals with first episode early-onset schizophrenia were significantly more impaired than patients with late-onset schizophrenia on digit symbol coding, but less impaired on auditory and visual attention, fluency, full-scale IQ and global measure of cognition (Rajji et al., 2009). From these findings, it appears that late-onset schizophrenia patients are particularly impaired in tests of auditory and visual attention, whereas their processing speed (measured by digit symbol coding) is relatively spared when compared to younger patients with schizophrenia. Conclusions regarding the comparisons on other tests are less clear and may be related to the fact that duration of illness and age, which differed between groups, were not controlled for. Cross-sectional studies that compared late-onset patients to similarly aged patients with early-onset schizophrenia found essentially similar neuropsychological deficit scores between the groups (Jeste et al., 1995; Sachdev et al., 1999). However, a more recent study by Vahia et al. (2010), which involved a much larger sample size, detected better performance on tests of processing speed, abstraction/cognitive flexibility and verbal memory in their late-onset patients compared to age-matched early-onset schizophrenia patients, but found no difference on tests of crystallized verbal knowledge and inconsistent results on the two tests of perceptual-organizational skill. Yet, when the duration of illness was controlled for, the differences in abstraction/cognitive flexibility and verbal memory became non-significant, leaving processing speed the only remaining significant difference between groups (Vahia et al., 2010). It appears that processing speed is more impaired in early-onset schizophrenia compared to late-onset schizophrenia regardless of age or chronicity of illness (Rajji et al., 2009; Vahia et al., 2010). With the possible exception of chronically institutionalized

elderly patients who do appear to have increased rates of dementia, the cognitive deficits in schizophrenia have been shown to be largely stable over the course of illness (Jeste, Wolkowitz & Palmer, 2011). Evidence to date points to a gradual decline with age that parallels the decline seen in the general population in terms of processing speed, episodic memory and executive function with a relative preservation of crystallized verbal knowledge (Jeste et al., 2011). However, it is unclear whether this pattern also applies to the late-onset psychotic group, in light of recent evidence demonstrating an association with dementia (discussed in detail below). Further study is necessary to better understand the relative contributions of the ageing process, underlying disease mechanisms, chronicity of illness, effects of medication and other factors such as cerebrovascular disease to the development of cognitive deficits and their pattern over time in late-onset psychotic disorder.

Neuroanatomical findings

The most robust findings on CT and MRI imaging of patients with schizophrenia (as reviewed by Shenton, Dickey, Frumin & McCarley, 2001) and late-onset psychotic disorder (as reviewed by Pearlson, 1999) are enlargement of the lateral and third ventricles, believed to indicate a tissue loss of the surrounding brain areas (e.g., temporal, frontal). The temporal lobes, hypothesized to be involved in the development of auditory hallucinations, thought disorganization and cognitive deficits in schizophrenia, have also consistently been shown to be smaller in volume. This seems to particularly affect the sub-structures of the hippocampus-amygdala complex, the superior temporal gyrus and

the planum temporale (Shenton et al, 2001). A much smaller number of MRI studies examining the temporal lobe structure in late-onset psychotic patients are available and their results have been inconsistent with both smaller volumes (Barta et al., 1997; Sachdev et al., 1999; Rabins, Aylward, Holroyd & Pearlson, 2000) and no differences (Howard et al., 1995a; Corey-Bloom, Jernigan, Archibald, Harris & Jeste, 1995) compared to age-matched healthy controls being reported. The findings of volume loss in other cortical brain regions (e.g., frontal, parietal, occipital lobes) in schizophrenia have been less robust (Shenton et al., 2001) and the only available studies in late-onset psychotic disorder reported no difference in frontal lobe measurements compared to age-matched healthy controls (Corey-Bloom et al., 1995; Howard et al., 1995a; Sachdev et al., 1999). On the less specific measurement of "cortical sulci", greater atrophy was reported on MRI, compared to age- and gender-matched healthy controls (Rabins et al., 2000), but not on CT (Burns, Carrick, Ames, Naguib & Levy, 1987). Other findings that have been reported in schizophrenia by a small majority of studies include increased size of the basal ganglia and decreased size of the thalamus compared to healthy controls (Shenton et al., 2001). In late-onset psychotic disorder, no difference was detected in the size of the caudate and lenticular nuclei or the thalamus compared to age-matched controls (Corey-Bloom et al., 1995; Howard et al., 1995a).

Results from studies directly comparing late-onset case with similarly aged early-onset schizophrenia cases have demonstrated similarities, for the most part. No differences between these groups have been reported on the measurement of the lateral

and third ventricles (Pearlson et al., 1993; Corey-Bloom et al., 1995; Sachdev et al., 1999), temporal lobe (Pearlson et al., 1993; Corey-Bloom et al., 1995; Sachdev et al., 1999), frontal lobe (Corey-Bloom et al., 1995; Sachdev et al., 1999), cerebellum (Sachdev & Brodaty, 1999a), corpus callosum (Sachdev & Brodaty, 1999a) or cortical atrophy (Pearlson et al., 1993; Symonds et al., 1997; Sachdev et al., 1999; Tonkonogy & Geller, 1999). Exceptions include the finding of Tonkonogy and Geller (1999) of a significantly greater proportion of early-onset paranoid schizophrenia cases with 'moderate to severe' graded ventricular enlargement and cortical atrophy compared to age-matched late-onset "paranoid psychosis" cases. As well, Sachdev et al. (1999) reported a significantly greater mid-parietal atrophy in late-onset schizophrenia compared to their early-onset counterparts. Corey-Bloom et al. (1995) reported an enlarged thalamus compared to age-matched early-onset schizophrenia patients, which has been suggested to reflect a relative decreased size in early-onset illness (Corey-Bloom et al., 1995; Shenton et al., 2001). In a direct comparison to patients with late-life affective disorder, patients with late-onset psychotic disorder had significantly larger temporal horns and third ventricles, whereas the former had significantly more atrophy of the superficial cortical sulci (Rabins et al., 2000).

There have been mixed results as to whether late onset psychotic disorder is associated with increased white matter hyperintensities (WMH) and/or vascular insults compared to age-matched healthy controls. WMH are common in the general population with one study reporting that in a group of "young-old" adults (aged 56 to 72), 11% and

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21% had some degree of WHM in the centrum semiovale and periventricular regions, respectively (Ylikoski et al., 1995). These proportions were considerably higher in "old-old" adults (aged 77 to 88) with 38% and 65% of this group having some degree of WHM in the centrum semiovale and pereiventricular regions, respectively (Ylikoski et al., 1995). In young (less than age 65) healthy patients who have been carefully screened for medical comorbidities, e.g., neurological disorders, cardiovascular disorders, diabetes and substance abuse, the presence of any WMH is quite rare (5.3%) and when present, tend to be small (Hopkins et al., 2006). WMH are strongly associated with age (DeCarli et al., 2005) and cardiovascular risk factors (Jeerakathil et al., 2004). Histopathological studies have revealed that WMH reflect a range of tissue changes such as partial loss of myelin, axons and oligodendroglial cells; astrogliosis; dilatation of perivascular spaces; activated macrophages and fibrohyalinotic vessel changes, that collectively suggest incomplete infarcts (Gouw et al., 2011). Current evidence points to an underlying ischaemic pathogenesis, although possible alternative mechanisms include altered cerebral blood flow autoregulation, axonal depletion from Wallerian degeneration and toxic effects of amyloid deposition on vasculature permeability (Gouw et al., 2011). A recent meta-analysis demonstrated the association between WMH and an increased risk of stroke, dementia and death (Debette & Markus, 2010). Remarkably, WMH volume has even been shown to predict cognitive decline at one-year follow-up in a relatively healthy sample of non-demented individuals (Carmichael et al., 2010).

Although there have been reports of a greater overall number of abnormal scans, including the presence of "large" sized white matter lesions and/or single or multiple strokes (Miller et al., 1992) and a greater number of signal hyperintensities in both the periventricular and the thalamic regions (Sachdev & Brodaty, 1999b) in late-onset psychotic disorder patients compared to age- and gender- matched healthy controls, other studies have failed to detect any difference in the presence of WMH between these two groups (Howard et al., 1995b; Corey-Bloom et al., 1995; Symonds et al., 1997; Rivkin et al., 2000). The discrepancy in findings may be due to the differences in the sensitivity of the machine being used, the way in which WMH are measured or in the samples of patients/controls between studies (Howard et al., 1995b).

Inconsistent results have also been reported in studies comparing late-onset psychotic disorder patients to similarly aged early-onset schizophrenic patients. Sachdev and Brodaty (1999b) reported that the late-onset schizophrenia group had more signal hyperintensities in the periventricular area and thalamus than old, education- and gender-matched, early-onset patients, even when taking into account the younger mean age of the early onset group. Notably the two schizophrenia groups did not differ significantly in cerebrovascular risk factors (e.g., hypertension, cardiovascular disease, diabetes, prior strokes/transient ischaemic attacks, family history of stroke) (Sachdev & Brodaty, 1999b). Similarly, Tonkonogy and Geller (1999) reported a significant increase in the severity and extent of WMH in the periventricular and deep white matter regions in late-onset compared to age-matched early-onset patients who were similar in terms of

education and cerebrovascular risk factors. On the other hand, Corey-Bloom et al. (1995) did not detect differences in the presence of white matter abnormalities between late-onset and early-onset groups matched for age, gender and education, although the sample sizes were noted to be quite small (i.e., n=14 and n=16). Symonds et al. (1997) also did not find a difference in the presence of infarcts or on the severity of WMH between similarly matched late-onset and early-onset groups, however, this study evaluated the severity of WMH based on the standard clinical dictations notes of neuroradiologists who were not blind to diagnosis or given any special instructions as to what to comment on. This is in contrast to the approach taken in the Sachdev et al. (1999) and Tonkonogy and Geller (1999) studies, which employed two blinded expert raters that were asked to directly measure WMH on MRI using validated scales. Rivkin et al. (2000) examined a small group of late-onset patients (n=12) and also failed to find a statistically significant difference in the total volume 'load' of WMH compared to early-onset cases that were of similar age, although this study appears to have been under-powered. Inconsistent results among the relative small number of studies make it rather difficult to draw any definite conclusions about WMH and their association with late-onset psychotic disorder. Further study with larger sample sizes, using the most reliable and sensitive measurement tools currently available are required in order to better our understanding the role WMH may play in the development of psychotic and cognitive symptoms, and to examine the possibility of an association with the subsequent development of dementia (see below).

Treatment response

Howard et al. (2000) summarized, from a review of seven open studies, dating back to 1966, that 48%-61% of late-onset psychotic patients achieve full remission of their symptoms when treated with neuroleptics. A lower full response rate (26%) was reported in a study involving a mix of care settings and a wide range of neuroleptic preparations (Howard & Levy, 1992). The depot route of administration was strongly associated with a positive treatment response and the involvement of a community psychiatric nurse showed a trend towards significance with respect to recovery (Howard & Levy, 1992). Factors such as neuroleptic dose, level of patient care, presence of hallucinations or first rank symptoms age or age of onset did not have a significant effect on treatment response (Howard & Levy, 1992). It has been consistently demonstrated that late-onset patients, require lower doses of antipsychotics compared to early-onset cases even when matched for age (e.g., Rodriguez-Ferrera et al., 2004; Uchida et al., 2008; Huang & Zhang, 2009; Vahia et al., 2010). According to a recent Cochrane Review, however, there is no evidence from well-devised clinical trials to guide clinicians in their treatment of these patients (Arunpongpaisal, Ahmed, Aqeel & Suchat, 2003). The authors could find no studies that met inclusion criteria for the review and the only randomized study that focused on late-onset schizophrenia involved two agents that have since been withdrawn from the market (Arunpongpaisal et al., 2003). Recently, Psarros, Theleritis, Paparrigopoulos, Politis and Papadimitriou (2009) published a preliminary open label study of 5 weeks duration, which demonstrated efficacy (i.e., significant change on BPRS, PANSS and CGI) for amisulpride in 26 patients with onset over 60 years old (mean age 76.2 years). A slight, but not significant, increase in extrapyrimidal symptoms

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was recorded. In 2011, Scott, Greenwald, Kramer and Shuwall determined, on the basis of a chart/electronic record review, that 38% of 8 outpatients and 77% of 13 inpatients with onset of psychosis over 60 years of age met criteria for a positive treatment response (e.g., clinician-based judgement of some degree of sign/symptom amelioration) to one of several second generation antipsychotics (e.g., risperidone, quetiapine, aripiprazole, olanzapine). To date, no randomized double-blind placebo-controlled trial of antipsychotic treatment in patients with late-onset psychotic disorder has been published. In summary, it is thought that a substantial proportion of patients with late-onset psychotic disorder can achieve a positive, if not full, treatment response using relatively low doses of antipsychotic medications. The response may increase with depot preparation. Further controlled trials are warranted to better understand the efficacy and tolerability of different antipsychotic medications and preparations, as well as the course of treatment in regards to duration, relapse and chronicity.

Course of illness

Overall, there is a notable dearth of information with respect to long-term course of illness in patients with late-onset psychotic disorder. Post (1966) followed a series of 65 patients over the age of 60 (with onset of paranoid symptoms after age 50) over a 14-21 month period. All had received anti-psychotic treatment. He observed that approximately a third remained symptom free, just over a third experienced symptoms for varying periods and the remaining had persisting psychotic symptoms. Jørgensen & Munk-Jørgensen (1985) reported, based on a retrospective chart review, that three

quarters of their late-onset "paranoid psychosis" patients (i.e., first referred for admission at age 60 or above with ICD-8 diagnoses of schizophrenia, paranoid state, reactive psychosis or "other psychosis") (n=106) were discharged home after their initial admission, while the remaining were transitioned to a nursing home. Over an average observation period of 10 years from the time of first admission, only one quarter of patients were fully remitted and the remaining had residual psychiatric symptoms over the period of observation or at death (Jørgensen & Munk-Jørgensen, 1985). Another study (n=42) found that, after an average of 3.7 years, approximately half of patients remained on continuous neuroleptic treatment, with 60% having resolution of the initial psychotic symptoms that had brought them to care (Hymas, Naguib & Levy, 1989). Based on Danish case register data, Riecher-Rössler et al. (1997) compared the 10 year course of patients with an index admission of schizophrenia before age 40 to those with an index admission of schizophrenia between ages 40 and 60. Late-onset cases had a significantly lower mean number of hospitalizations, a shorter duration of hospitalization and a significantly longer time prior to rehospitalization after the index admission compared to early-onset cases (Riecher-Rössler et al., 1997). The fact that patients with late-onset were more likely to be married was thought to have contributed to their better outcomes with regards to hospitalization (Riecher-Rössler et al., 1997). Interestingly, late-onset females tended to have a poorer course (i.e., spent more days in hospital) than late-onset males, whereas the opposite finding of males having a poorer course was observed for early-onset cases (Riecher-Rössler et al., 1997). In a prospectively designed longitudinal study (n=19), of the sub-group of patients who remained living and could be personally

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assessed by the investigators (n=7) at 5 year follow-up, 86% continued to have some degree of psychosis, although only one patient continued to meet criteria for schizophrenia (Brodaty, Sachdev, Koschera, Monk & Cullen, 2003). In terms of mortality, patients with late-onset schizophrenia (onset over age 44) were no more likely to have died at 120 month follow-up than patients with late-life major depressive disorder but significantly less likely than patients with dementia and secondary psychosis (Rabins & Lavrisha, 2003). Recently, mortality has been reported to be 2-3 times higher in late-onset patients compared to healthy controls or the general population (Jeste et al., 1997; Kørner, Lopez, Lauritzen, Andersen & Kessing, 2008; Kørner, Lopez, Lauritzen, Andersen & Kessing, 2009), although earlier studies did not detect a difference (Kay, 1972; Hymas et al., 1989). The research on long-term outcomes of late-onset psychotic disorder is limited to prospective studies with small sample sizes and retrospective studies relying on case register data. Despite these limitations, it appears that patients with late-onset may have a comparatively better course than early-onset cases with regards to hospitalization, despite ongoing psychosis. Mortality rates for patients with late-onset psychotic disorder appear to lie in between the relatively higher rates for patients with dementia and "secondary" psychosis, and the rates for the general population, and are comparable to patients with late-life depression.

Is late-onset psychotic disorder a prelude to dementia?

One area of particular attention, in the study of late-onset psychotic disorder, is whether it might be a prodrome to progressive cognitive decline or dementia, as has been

reported with late-onset depression (Schweitzer, Tuckwell, O'Brien & Ames, 2002). Positive findings in this regard would support the disorder as a neurodegenerative (versus neurodevelopmental) process. However, not unlike the variety of age-cut offs and the confusing array of terms used to describe late-onset psychotic disorder patients in the research literature, the cognitive status criteria (i.e., how to exclude patients with dementia in this group) are also notably inconsistent. Many studies require a certain cut-off MMSE or similar mental test score (e.g., Holden, 1987) for inclusion, although these too can be quite variable, e.g., a cut-off of 20 or greater (Brodaty et al., 2003) compared to a cut-off of 24 or greater (Howard, Almeida, Levy, Graves & Graves, 1994b), which is the commonly accepted cutoff score used in clinical settings to detect cognitive impairment. Other studies exclude patients on the basis of a clinical diagnosis of dementia (e.g., Jørgensen & Munk-Jørgensen, 1985; Laks, Fontenelle, Chalita & Mendlowicz, 2006; Kørner et al., 2008; Kørner et al., 2009) and some lack any specific exclusion criteria regarding cognitive status (e.g., Huang & Zhang, 2009). Given this variability, it is not surprising that cognitive scores in study samples range from a mean MMSE score of 17.6 (Huang & Zhang, 2009) to 28.21 (Howard et al., 1994b). The variability, among studies, in how patients are initially included or excluded with respect to cognition poses a significant challenge to one's understanding of whether or not a diagnosis of late-onset psychotic disorder carries a risk of cognitive decline beyond age matched controls.

Jørgensen & Munk-Jørgensen (1985) determined that 26% of their late-onset "paranoid psychosis" patients were re-referred for admission over a mean follow-up time of 48 months (taking into account deaths) and in approximately one-third of these re-referred patients, their clinical diagnosis was changed to dementia. The authors suggested that this was due to the appearance of new cognitive symptoms rather than a re-conceptualization of previous diagnosis. Based on retrospective chart review of the patient's clinical state and an unspecified mental test score, Holden (1987) determined that 35% of patients in his series of new late paraphrenia cases progressed to dementia within three years – a group he would refer to as "organic" and would consider distinct from the "functional" late paraphrenics. He found no differences in the characteristics at presentation between the two groups, with the exception that the former had relatively lower scores on a questionnaire of orientation, memory and general knowledge at the outset, which suggests they may have already been demonstrating a prodomal mild cognitive impairment. Based on a 1 to 2 year follow-up period, Palmer et al. (2003) found no difference in the performance of community-dwelling late-onset psychotic disorder patients (n=37) on the Mini-Mental State Examination (MMSE) or the Mattis Dementia Rating Scale (DRS) over time compared to age-matched early-onset patients (n=71) and normal controls (n=56). A pilot study looking at cognitive change in late-onset schizophrenia patients (n=13) reported no significant change from baseline to 1 year follow-up on the MMSE or on another examination that assesses the same domains with more depth (e.g., the CAMCOG) in patients with onset over age 50 (Laks et al., 2006). However, this study was limited methodologically in that it included patients at baseline

that had mean scores consistent with mild cognitive impairment/dementia (e.g., mean

MMSE = 21). This particularly low baseline mean score likely reflects the fact that the

recruited sample population was patients attending the outpatient clinic for Alzheimer´s

Disease and related disorders, and may point to the possibility that cognitive deterioration

has already occurred based on the sample's mean (SD) duration of illness of 6.69 (±6.13)

years.

At 5-year follow-up, Brodaty et al. (2003) were able to report on outcomes in 70%

of their initial baseline sample of 27 late-onset schizophrenia patients (50 years or older)

and a similar proportion of their 34 healthy controls who had significantly more years of

education – a potential confounder - but were otherwise comparable on age, gender and

socioeconomic status. The patient group was more likely to be institutionalized at an

earlier mean age (79 years versus 86 years) and to experience a greater decline on

measures of cognition (e.g., Clinical Dementia Scale, MMSE) and instrumental/activities

of daily living scores. Just over half (9 out of 19) of the patient group met DSM-IV

criteria for dementia at 5 years including dementia of Alzheimer's type (5), vascular

dementia (1) and unknown type (3), compared to none of the controls (n=24). Post-hoc

analysis demonstrated a trend for those who went on to develop dementia to be older at

baseline and to have lower socioeconomic status, a longer duration of illness, poorer

performance in their Activities of Daily Living (ADLs) and Instrumental ADLs (IADLs)

and MMSE at baseline, higher VBR and more WMH on MRI. Ostling et al. (2007) also

reported an increased rate of dementia in those who presented with first-onset primary

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psychotic symptoms over the age of 70 compared to those did not develop psychotic symptoms over the course of a 20-year follow-up period (Hazard Ratio = 3.5). The presence of hallucinations, particularly of the visual type, significantly predicted the development of dementia at a mean interval 5.0 years (SD 4.7).

Using Danish register data, Kørner et al. (2009) found that over a median follow up period of 3 to 4 years, patients with late-onset schizophrenia (first-contact over age 40) (n= 1,206) and very-late-onset schizophrenia (first contact over age 60) (n=409) were both three times more likely to be diagnosed with dementia (a combination of Alzheimer's disease, vascular dementia and unspecified types) than patients with osteoarthritis (adjusted for age and calendar time), and twice more likely to be diagnosed with dementia than a gender-, age-, and calendar-matched sample of the general population. This study was limited by a lack of available information on treatment, social circumstances, educational level, and other demographic variables that may have contributed to the development of dementia. Using the same methodological approach, Kørner et al. (2008) determined that patients with a diagnosis of very-late-onset delusional disorder (first contact over the age of 60) (n=1,437) were eight times more likely to be diagnosed with dementia (15.2% versus 2.1%) compared to those with a diagnosis of osteoarthritis (adjusted for age at first contact, gender, duration of illness, a diagnosis of substance abuse and calendar time) over a median follow-up period of approximately 2 and 4 years, respectively. Compared to a gender-, age-, and calendar-matched sample of the general population, very-late-onset delusional disorder were 5

times more likely to be diagnosed with dementia. Notably the period of highest risk of being diagnosed with dementia in patients with initial diagnosis of delusional disorder was in the first 6 months, which the authors suggest may reflect the obscuration of underlying dementia by the delusions (Kørner et al., 2008). Nevertheless, the authors pointed out that even after a 12-month follow-up period, female and male patients with delusional disorder were still 4 to 8 times more likely, respectively, to be diagnosed with dementia. Although to our knowledge longer-term dementia outcome studies directly comparing late-onset psychotic disorder patients to older early-onset patients do not exist at this time, the evidence to date suggests that early-onset schizophrenia, with the minor exception of chronically institutionalized patients, is not associated with a greater than age-expected cognitive decline and conversion to clinical dementia (Jeste et al., 2011). Two small studies comparing late-onset psychotic disorder patients to patients with late-life major depressive disorder found no difference in the likelihood of developing dementia within 7 to 10 years (Rabins & Lavrisha, 2003; Leinonen et al., 2004).

In summary, the studies that have had sufficiently long follow-up periods have demonstrated an increased rate of dementia for late-onset psychotic disorder compared to normal controls, but not necessarily to late-life depression. Further study is required to directly compare the rate of dementia with early-onset schizophrenia patients as they age and to determine the existence of particular predisposing factors or a sub-group within late-onset psychotic disorder associated with the development of dementia.

Neuropathological findings

In terms of neuropathology, Casanova, Stevens, Brown, Royston and Bruton (2002) found an increased presence of neurofibrillary tangles (although not at the level consistent with a diagnosis of Alzheimer's dementia) in late-onset schizophrenia patients (onset over age 40) (n=34) compared to normal controls (n=18) and old early-onset schizophrenia patients (onset younger than age 40) (n=30), but only the former comparison reached statistical significance. Neurofibrillary pathology in late-onset schizophrenia patients was predominantly limited to the transentorhinal cortex, entorhinal region, subiculum and the CA1 subfield of the anterior hippocampus. Notably, amyloid deposits were sparse or absent, and there was no difference compared to controls on cell loss. However, this study was limited by the retrospective diagnosis of schizophrenia, the seeming lack of any process to exclude the presence of cognitive impairment and by the potential confounder of age (e.g., late-onset patients had an older mean age at death than the other two groups). Nevertheless, Casanova (2010) suggested that these findings are consistent with a diagnosis of Neurofibrillary Tangle-Predominant form of Senile Dementia (NFT-SD), a condition reportedly seen in extreme old age that is associated with slowly progressive cognitive decline leading to a mild form of dementia.

The current diagnostic status of late-onset psychotic disorder

In 1998, the International Late-Onset Schizophrenia Group made up of seventeen experts in the field of late-onset psychosis met over a two-day period with the aim to develop a consensus statement clarifying the diagnosis and nomenclature as well as the

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treatment guidelines and future directions (Howard et al., 2000). Upon review of the

literature and much discussion, Howard et al. (2000) recommended the following

diagnostic categories: late-onset schizophrenia (if symptom development after age 40)

and very-late-onset schizophrenia-like psychosis (if symptom development after age 60)

and to abandon the once prevalent diagnosis of late paraphrenia. However, Howard et al.

(2000) recognized that the "available data suggest that categorization by specific age at

onset ranges is relatively arbitrary" reflected by the fact that unanimity could not be

reached by this group of experts on either the presence of age cut-offs or where they

ought to be set (Howard et al., 2000). Subsequently, the only study to date to directly

compare these two proposed age categories on clinico-demographic and symptom

variables fails to support their differentiation (Girard & Simard, 2008). A further issue is

that the diagnostic criteria associated with Howard et al. (2000) proposed categories were

not clearly outlined, which has led to their variable use (e.g., Reeves et al, 2001; Alici-

Evcimen et al., 2003; Girard & Simard, 2008; Vahia et al., 2010). Specifically, the

suggested diagnoses of late-onset schizophrenia and very-late-onset schizophrenia-like

psychosis fail to address the role and place of other diagnostic categories within late-onset

psychosis, in particular, that of delusional disorder, despite the fact that patients

previously referred to as late paraphrenia meet criteria for either schizophrenia or

delusional disorder (Quintal, et al., 1991; Almeida et al., 1995a). This lack of clarity has

lead to the recent publication of studies that combine the diagnosis of schizophrenia with

that of delusional disorder (Rodriguez-Ferrera et al., 2004; Girard & Simard, 2008),

schizophreniform disorder (Girard & Simard, 2008), schizoaffective disorder (Rodriguez-

Ferrera et al., 2004; Huang & Zhang, 2009; Vahia et al., 2010) and nonspecific psychotic disorder (Girard & Simard, 2008) under the umbrella terms of "late-onset schizophrenia" and/or "very-late-onset schizophrenia-like psychosis". Notably, these recommended categories (Howard et al., 2000) were not included in the last revisions of the DSM-IV (APA, 2000) or ICD-10 (WHO, 2007).

In summary, there is currently no independent codeable diagnosis for patients presenting with primary late-onset psychosis, within DSM or ICD. If a cognitively intact person, 40 years of older was to present with a non-affective, primary psychotic disorder of at least one month duration, they would invariably be diagnosed as having either schizophrenia or delusional disorder.

Applying the diagnoses of schizophrenia and delusional disorder to late-onset patients

Although it may be the case that late-onset psychotic disorder patients can be classified as either schizophrenia or delusional disorder using current diagnostic criteria (Quintal et al., 1991; Almeida et al., 1995a) it is unclear as to whether these diagnostic categories are in fact valid and/or useful in the late-onset psychotic population (Jørgensen & Munk-Jørgensen, 1985; Quintal et al., 1991; Howard et al., 1994a; Almeida et al., 1995a; Evans et al., 1996; Roth & Kay, 1998; Riecher-Rössler et al., 2003). First, there are the conflicting points of view regarding the nature of the relationship between schizophrenia and late-onset psychotic disorder, that is, some say they are the same disorder, others say they are fundamentally distinct. Secondly, there is the question of

whether the differences in the current diagnostic criteria for schizophrenia and delusional become more or less arbitrary when applied to the typical late-onset presentation. Lastly, studies that have attempted to directly compare these diagnostic sub-groups within the overall group of late-onset patients, have failed to detect significant differences on a host of variables, raising questions about the validity of making such a distinction.

What is the relationship between late-onset psychotic disorder and schizophrenia?

On one hand, the most widely held approach, both historically and currently, has been to conceptualize late-onset psychotic disorder as the manifestation of schizophrenia in older age (Bleuler, 1943; Fish, 1960; Kay & Roth, 1961; Grahame, 1984; Pearlson et al., 1989; Riecher-Rössler et al., 1997) and as such, it should be formally referred to as a variant or subtype of schizophrenia, e.g., "late-onset schizophrenia" and "very-late-onset schizophrenia-like psychosis" (Howard et al., 2000; Vahia et al., 2010). Howard et al. (2000) concluded that "schizophrenia continues to be an illness of mysterious causation that usually strikes in adolescence or early adulthood but may uncommonly affect children or express itself for the first time in middle or late life." In the consensus statement, Howard et al. (2000) emphasized the similarities in positive symptoms, cognitive deficits and non-specific brain imaging findings between the different ages of onset as well as the lack of evidence (at the time) in terms of an association of late-onset psychotic disorder with a progressive dementing disorder.

On the other hand, late-onset psychotic disorder has been proposed to be a distinct disorder from "classic" schizophrenia and therefore, it should not be labeled as such (Almeida et al., 1992; Andreasen, 1999). The preeminent schizophrenia researcher, Nancy Andreasen, argued in her chapter titled "I don't believe in Late Onset Schizophrenia" (1999) that in the absence of known etiological factors (the "gold standard" in the identification of a disease) or pathophysiological mechanisms (the "silver standard") for schizophrenia, "it is important to maintain a clear concept of the disorder at the clinical or phenomenological level". However, what is considered to be "pathognomonic" for schizophrenia has never been entirely clear (Flaum & Schultz, 1996). This has directly played into the confusion surrounding late-onset psychotic disorder diagnostics. An example of this is the role of the Schneiderian first-rank symptoms in the diagnosis of (late-onset) schizophrenia. The DSM-IV-TR (APA, 2000) has included certain first-rank symptoms (e.g., a voice commenting on thoughts/behaviour or voices arguing) to be the most highly weighted criteria for schizophrenia. The presence of first rank symptoms in late-onset psychotic disorder patients has been used to justify the use of the diagnosis of schizophrenia in these patients (e.g., Post, 1966; Grahame, 1984). However, more recent work had failed to indicate any construct level validity in distinguishing between late-onset patients with or without first rank symptoms (Riecher-Rössler et al., 2003). Furthermore, exhaustive review of the literature on first-rank symptoms has concluded that they are not necessarily specific to schizophrenia (regardless of age) and do not deserve the emphasis that they have been

given in the current editions of the DSM and ICD (Nordgraad, Arnfred, Handest & Parnas 2008).

According to Andreasen (1999), in keeping with what was first described by Kraepelin, "there is a concept or idea of schizophrenia that many of us who study this disorder hold in our minds and use when we diagnose patients clinically or when we design research studies. This idea has to some extent been operationalized in the diagnostic criteria we currently use…[It] include[s] negative symptoms as well as positive psychotic symptoms…deterioration in function during time period around its onset, and that people with schizophrenia do not have a restituo ad integrum after they become ill". Defined as such, with emphasis placed on the presence of negative symptoms and disorganization, the schizophrenia syndrome has "a characteristic onset in late adolescence or early adult life" (Andreasen, 1999). Andreasen (1999) wholly acknowledged that people can develop psychotic symptoms for the first time in late life, but that they tend to present solely with delusions and hallucinations, whereas negative symptoms, such as affective blunting, and formal thought disorders are typically absent. Hence, she concluded that such patients have a "psychotic disorder", but not schizophrenia (Andreasen, 1999).[2] Almeida et al. (1995a) similarly pointed out that

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[2] On a side note, as a further demonstration of the confusion that surrounds late-onset psychotic disorder, arguments similar to Andreasen's have been articulated (Almeida et al., 1995a; Taylor, 2001) in a plea to maintain the diagnostic category of late paraphrenia instead of late-onset schizophrenia – although late paraphrenia was originally conceptualized by Kay and Roth (1961) to be the manifestation of schizophrenia in old age.

Criterion A is easily met by most late paraphrenia patients, who often have prominent

hallucinations and delusions, "although this is clearly not enough to define consistently a

disorder as complex as schizophrenia." Instead, Andreasen (1999) argued for the need to

examine the differences between late-onset psychotic disorder and schizophrenia at other

"levels of identification of diseases". This includes the observations that the clinical

presentation tends to be more variable at early-onset and more homogenous at later-onset,

and a shift to a higher ratio of females, a reduction in the genetic loading of schizophrenia

and possibly better response to neuroleptic treatment with later-onset. As earlier

reviewed, late-onset psychotic disorder also differentiates from early-onset schizophrenia

in having better premorbid and possibly post-onset functioning, less family history of

schizophrenia, lower doses of antipsychotic medication (even when matched for age) and

less hospitalization. There are also preliminary findings showing differences on certain

neuroanatomical structures, e.g., the mid-parietal region and thalamus. Furthermore,

Andreasen (1999) believes that late-onset psychotic disorder must be due to a

neurodegenerative process, in contrast to the commonly held notion that schizophrenia is

a neurodevelopment disorder (Rapoport et al., 2005). The question of whether late-onset

psychotic disorder is neurodegenerative versus neurodevelopmental has been widely

discussed with a range of views being presented (e.g., Jeste et al., 1997; Howard &

Rabins, 1997; Pearlson, 1999; Palmer et al., 2003; Lagodka & Robert, 2009; Vahia et al.,

2010; Casanova, 2010). For instance, it has been suggested that late-onset schizophrenia

may represent delayed expression of early onset illness that manifests in the context

neurobiological changes in mid or late life, such as a the loss of earlier protective factors

and/or an accumulation of risk factors (Palmer et al., 2003; Vahia et al., 2010). Others suggest that although this may be the case for "mid-life" illness (i.e., age 45 to 60), those which begin after the age of 60 years are more likely to be "phenocopies" of schizophrenia with a neurodegenerative etiology (Howard & Rabins, 1997). There is also the view that it is a "mild" form of schizophrenia (Palmer et al., 2003). The argument, of course, cannot be definitively solved until the underlying pathobiologies are actually identified. The findings of an association between late-onset psychotic disorder and the subsequent development of dementia offer the strongest support for this condition being neurodegenerative as opposed to neurodevelopmental in nature.

In some ways, it could be argued that the International Late-Onset Schizophrenia Group consensus statement (Howard et al., 2000) does not necessarily contradict the arguments proposed by Andreasen (1999). Rather, the difference in conceptualizations seems to rest in *how* the term schizophrenia is used. The diagnosis of schizophrenia was justified for use with late-onset patients by the International Late-Onset Schizophrenia Group given their emphasis on a more flexible conceptualization of schizophrenia (in keeping with the Bleurelian tradition), evidenced by their use of the term "schizophrenia-like psychoses" and the statement that "the expression of such psychotic symptoms shows greatest *variation* when onset age is at both extremes of life" (my italics; Howard et al., 2000). Vahia et al. (2010) similarly stated that "despite important differences", "LOS [late onset schizophrenia] and EOS [early onset schizophrenia] show sufficient overlap to warrant consideration as a single disorder (commensurate with the *heterogeneity* between

and within other schizophrenia subtypes)" (my italics). Pearlson, another prominent researcher in the field, continued to use the term, schizophrenia, for late-onset cases, despite his doubts about there being a common etiopathophysiological mechanism. He wrote, "it remains possible, but unlikely, that both early and late onset forms of schizophrenia represent the same disorder in the sense of sharing the same aetiopathogenesis" (Pearlson, 1999, p.198). Clearly, this is in contrast to the narrower conceptualization (in keeping with the Kraepelin approach) of what constitutes schizophrenia as outlined by Andreasen (1999). The debate seems to also rest on the perceived utility of maintaining the term schizophrenia. Some have argued that maintaining the diagnosis of schizophrenia for late-onset psychotic disorder patients could lead to difficulties identifying patients for research purposes (Quintal et al., 1991; Andreasen, 1999) and confusion at the clinical level (Andreasen, 1999). Whereas the International Late-Onset Schizophrenia Group consensus statement claimed that "variations in epidemiology, symptomatology, pathophysiology, and treatment response with age of onset can help to provide important clues to causative risk factors" of schizophrenia (Howard et al., 2000).

Are there differences between the diagnostic criteria of schizophrenia and delusional in the late-onset context?

The DSM diagnostic criteria for both schizophrenia and delusional disorder (see Appendix 1) are centered on phenomenology. In both disorders, the presence of delusions +/- hallucinations is sufficient to meet "Criterion A". However, in the criteria for

delusional disorder, it is stipulated that the delusions must be non-bizarre. Furthermore,

the DSM-IV-TR criteria allow for olfactory and tactile hallucinations in delusional

disorder if they relate to the delusional theme, and other hallucination modalities (e.g.,

auditory, visual) as long as they are "non-prominent". It should also be noted that current

DSM criteria states that the presence of bizarre delusions (and no other symptoms) is

sufficient for Criterion A of schizophrenia to be met. Late-onset psychotic disorder

patients characteristically present only with the positive symptoms (delusions and/or

hallucinations of varying severity and themes/modalities) of psychosis, and not catatonia,

thought disorganization, affective blunting or flattening, or other significant negative

symptoms that make up the remaining symptom criteria for schizophrenia. This means

that the distinction between making the diagnosis of schizophrenia versus delusional

disorder in late-onset patients essentially falls on the rather subjective and arbitrary

determination of whether auditory or visual hallucinations are "prominent" or not and

whether a delusion is "bizarre" or not. This state of affairs is clearly problematic. There is

no guidance in the diagnostic manuals as to how "prominence" is to be determined. With

respect to the 'bizarreness' of delusions this has been defined in DSM IV as those that are

"clearly implausible and not understandable and do not derive from ordinary life

experiences". It has been pointed out, however, that given the considerable diversity

between ethnic and cultural belief systems, and ongoing advances in modern technology,

it can be quite difficult to determine whether a belief is implausible or not (APA, 2000;

Goldman, Hien, Haas, Sweeney & Frances, 1992). Furthermore, recent studies have

failed to show adequate reliability or utility associated with the bizarreness of delusions (Goldman et al., 1992; Mojtabai & Nicholson, 1995; Cermolacce, Sass & Parnas, 2010).

Are there valid diagnostic distinctions between schizophrenia and delusional disorder within the late-onset population?

Few studies have attempted to compare the diagnostic sub-groups of delusional disorder and schizophrenia or similar categories (e.g., "paranoid psychosis") within the late-onset population (Jørgensen & Munk-Jørgensen, 1985; Holden, 1987; Flint, Rifat & Eastwood, 1991; Yassa & Suranyi-Cadotte, 1993; Howard et al., 1994a; Howard et al., 1994b; Howard et al., 1995a; Evans et al., 1996; Riecher-Rössler et al., 2003). Those that have been done are summarized in Table 1. Unfortunately, the amount of useful information that can be drawn from these studies is limited, not only as a result of their use of different diagnostic terms, criteria and age-cut-offs, but also because of methodological shortcomings including the retrospective nature of some, small sample sizes and a lack of statistical analysis. For instance, Riecher-Rössler et al. (2003) employed the more broadly constructed diagnostic group of "paranoid psychoses" based on ICD-8 and ICD-9 criteria and compared these individuals to those diagnosed with schizophrenia. However, in current nosology, a proportion of the "paranoid psychosis" group, which included the diagnostic category of paraphrenia (ICD-9 297.2), would meet criteria for schizophrenia. Therefore the two groups being compared both included patients with schizophrenia. In a similar manner, the study by Flint et al. (1991) that compared late paraphrenia patients to late-onset paranoia patients based on ICD-9 criteria,

would also likely have patients meeting current diagnostic criteria for delusional disorder allocated in the two groups. With the exception of the studies of Howard et al. (1994a; 1994b; 1995a), which utilized ICD-10 criteria, none have used the most current diagnostic criteria available. Although it is difficult to draw firm conclusions, due to the limitations outlined above, the majority of these studies failed to show consistent or meaningful differences that support a distinction between schizophrenia and delusional disorder of late-onset.

Table 1. Studies comparing schizophrenia and delusional disorder

Reference	Stated aim(s)	Methodology	Sample	Demographics	Psychiatric History and Medical Co-morbidity	Clinical characteristics	Neurological markers	Treatment and Outcome	Comments
1. Jorgensen & Munk-Jorgensen, 1985	To describe the nature of the delusions, their distribution according to diagnostic groups as well as the course of illness.	Registry review of first-referred patients to a psychiatric hospital from 1970-1979. Course of illness information obtained from general physician and/or admitting hospital. Average observation period = 10 yrs (5-15). $\geq$ 60 years old with Dx of ICD-8 SCZ (295), paranoid state (297), reactive psychosis (298), or other psychoses (299)	Total: n= 106 (31.1% M: 68.9% F, age x 72 yrs (60-94)) *Subgroups:* • SCZ (n=7) • paranoid states (n=50) • reactive psychoses (n=39) • other psychoses (n=10)	Sex: *NS* (c^2 = 1.94, df = 3, p=0.58)**		Type of delusions: *NS*		Full remissions with no relapses: reactive psychoses had significantly fewer than other groups (p<0.05) Dx change (n=28): 7 paranoid states to dementia; 2 reactive psychoses to dementia; 3 reactive psychoses to affective psychosis; 2 other psychoses to affective psychosis	ICD-8 diagnoses matched closely with DSM-III diagnostic categories of schizophrenia, paranoid states, reactive psychosis and other psychoses

Table 1 continued.

Reference	Stated aim(s)	Methodology	Sample	Demographics	Psychiatric History and Medical Co-morbidity	Clinical characteristics	Neurological markers	Treatment and Outcome	Comments
2. Flint et al., 1991	To examine the concept of paranoia beginning in old age and determine whether it differed from strictly defined LP.	Chart review of first-referred patients to tertiary care psychiatric institute from 1972-1987. ≥ 60 years old with Dx of ICD-8 295, 297 and ICD-9 SCZ (295) and ICD-9 PP (297,298.3/4/8)	Total: n= 33 (18.2% M: 81.8% F, age x 72 SD 9.5 yrs) *For the study, subjects were reclassified as:* • ICD-9 297.2 LP (n=21) • ICD-9 297.1 Paranoia (n=12)	Age: *NS* Sex: *NS* Never married: *NS* Social isolation: *NS*	Visual impairment: *NS* Hearing impairment: *NS* Cerebrovascular risk factors: *NS*	Type of delusions: *NS* Duration of delusions: *NS*	EEG abnormality (slow waves): *NS* CT brain (n=16): 4/4 paranoia *vs* 1/12 LP had subclinical cerebrovascular infarctions (p=0.003)	Neuroleptic dose: *NS* Tx duration: *NS* Side effects: *NS* Non-compliance: *NS* Full response: LP>paranoia	Reclassified patients with ICD-9 SCZ into either LP or paranoia based on the presence or absence of hallucinations. Small sample size for CT Did not account for potential confounders (e.g., age) in imaging subsample

Table 1 continued.

Reference	Stated aim(s)	Methodology	Sample	Demographics	Psychiatric History and Medical Co-morbidity	Clinical characteristics	Neurological markers	Treatment and Outcome	Comments
3. Yassa & Suranyi-Cadotte, 1993	Compare groups of late-onset paranoia and late-onset SCZ using Kraepelin's and DSM-III-R criteria on general characteristics and long-term follow-up	Prospective case series of patients ≥ 65 years old admitted to inpatient unit with late-onset (≥ 45 years old) SCZ and DD over a 7 year period. *For the study, subjects were reclassified as:* • DSM-III-R DD w/o H (n = 13) • DSM-III-R DD w/ H (n=7) • DSM-III-R SCZ (n=20)	Total: n= 40 (15% M: 85% F, x age N/A)	Sex: *NS* ($c^2 = 1.56$, df = 2, p=0.46)** Age at first admission: DD w/o H > DD w H, SCZ Current age: *NS* Marital status: *NS* ($c^2 = 4.3$, df = 6, p=0.64)** Educational status: *NS* ($c^2 = 6.7$, df = 6, p=0.35)** Premorbid personality: *NS* ($c^2 = 9.8$, df = 6, p=0.13)	Total duration of index hospitalization: *NS* Physical comorbidity: *NS* ($c^2 = 1.53$, df = 2, p=0.47)** Hypertension: NS between DD w/H and DD w/o H; DD w/o H > SCZ (p <0.05) Sensory deprivation: *NS*	Presence of FRS: only SCZ "Depressive symptoms": *NS* ($c^2 = 0.71$, df = 2, p=0.70)** Homicidality: *NS* ($c^2 = .41$, df = 2, p=0.82)** Suicidality: *NS* ($c^2 = 2.11$, df = 2, p=0.35)**	EEG disturbance: *NS*	"Remained stable" at follow-up (excluded deaths and lost to follow-up): *NS* # re-admissions: SCZ > DD w/o H	Did not provide statistics on a number of comparisons Absence of any standardized scales Single interview Small sample size
4. Howard et al., 1994a	1) To record the phenomenology of LP 2) To determine if its possible, based on symptoms, to separate LP into subgroups that differ on demographic and neuropsychological factors	Prospective case series of ≥ 60 years old inpatients, day-patients and outpatients diagnosed with LP. *For the study, LP was reclassified as:* • ICD-10 SCZ (n = 62) • ICD-10 DD (n = 31) • ICD-10 SCZA (n = 8)	Total: n= 101 (13.9% M: 86.1% F, age x 80 SD 6.3 yrs)	Current age: *NS* Age of onset: *NS* Sex: *NS* Never having married: *NS* Pre-morbid IQ: SCZ>DD (score 103.6 vs. 99.4 on the NART)		MMSE: SCZ>DD (score 27.6 vs. 25.6) PSE psychotic symptoms: SCZ>DD Insight: *NS*		Response to medication: *NS*	

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Table 1 continued.

Reference	Stated aim(s)	Methodology	Sample	Demographics	Psychiatric History and Medical Co-morbidity	Clinical characteristics	Neurological markers	Treatment and Outcome	Comments
5. Howard et al., 1994b	To quantify the volumes of brain and internal and external cerebrospinal fluid (CSF) in a large sample of patients with LP and HC.	Case-control MRI-brain study comparing a subgroup from LP sample described above to HC	Total: n= 50 (17% M: 83% F, age x 80 yrs) *For the study, LP was reclassified as:* • ICD-10 SCZ (n = 31) • ICD-10 DD (n = 19) HC: n= 35 (12% M: 88% F, x age 80 yrs)	Current age: DD>SCZ, HC (83.19 yrs *vs* 78.10 yrs *vs* 79.48 yrs) Age at onset: *NS*		MMSE: *NS*	Right lateral ventricle volume: *NS* between SCZ and HC; DD>HC Left lateral ventricle volume: *NS* between SCZ and HC; DD>HC Third ventricle volume: DD>HC		Acquired rateable scans from only 47 LP (31 SCZ, 16 DD) and 33 HC One-way ANOVA comparing volumetric measurements used age as a covariable. Detected differences were found between DD and HC, but no detected differences reported between DD and SCZ

Table 1 continued.

Reference	Stated aim(s)	Methodology	Sample	Demographics	Psychiatric History and Medical Co-morbidity	Clinical characteristics	Neurological markers	Treatment and Outcome	Comments
6. Howard et al., 1995	1) To determine whether structural differences between patients and HC are as subtle as differences seen with early-onset SCZ 2) To determine whether there are anatomical differences between subtypes SCZ and DD	Case-control MRI-brain study comparing a subgroup from LP to HC	As above	As above			Hippocampal, parahiccompal and superior tempora gyral volumes: *NS* Planar area of basal ganglia: *NS* Frontal and temporal lobe volumes: *NS* Degree of temporal lobe asymmetry: DD>HC		Comparisons were corrected for age. Reported a non-significant trend for DD to have smaller left temporal lobe volumes than SCZ and HC, but not when corrected for age.
7. Evans et al., 1996	Extend the delineation of DD and SCZ by use of a comprehensive neuropsychiatric evaluation	Prospective case series of outpatients with SCID based diagnoses of SCZ and DD with onset at 40 years or older	DSM-III-R SCZ: n = 50 (52% M: 48% F, age x 63.5 SD 8.9 yrs) DSM-III-R DD: n = 14 (42.9% M: 67.1% F, age x 66.9 SD 13.6 yrs)	Current Age: *NS* Age of onset: *NS* Sex: *NS* Education years: *NS* Marital status: *NS* Premorbid functioning (G-K scale): *NS*	Previous psych hospitalization: SCZ>DD FHx-psychosis: *NS* FHx-mood: *NS* Duration of illness: *NS*	BPRS total: DD>SCZ SAPS total: *NS* SANS total: *NS* Ham-D total: *NS* AIMS total: *NS* Multiple neuropsychological measures: *NS*		Frequency of neuroleptics: *NS* Daily neuroleptic dose: *NS* On follow-up (x 4 yrs) no DD or SCZ changed diagnosis	Patient sample recruited from DVA, a largely Caucasian male population. Power limited by small sample size for DD group (study reported some non-significant trends).

Table 1 continued.

Reference	Stated aim(s)	Methodology	Sample	Demographics	Psychiatric History and Medical Co-morbidity	Clinical characteristics	Neurological markers	Treatment and Outcome	Comments
8. Riecher-Rossler et al., 2003	To test the validity of the distinction between schizophrenia and paranoid states/delusional disorder	Registry review of first-admitted patients to a psychiatric hospital from 1978-1992. Patients were ≥ 40 years old with Dx of ICD-8 295, 297, 298.3 or ICD-9 295, 297, 298.3/4	ICD 8/9 SCZ: n = 199 (27.6% M: 72.4% F, age x 50 SD 9.1 yrs) ICD 8/9 PP: n= 153 (17.6% M: 82.4% F, age x 63.2 SD 12.4 yrs)	Age: PP > SCZ Sex: PP had more females than SCZ Acute social isolation: PP>SCZ Hx of extended separation in childhood: *NS*	Duration of Sx prior to adm: SCZ>PP Previous psych Tx for other Dx: SCZ>PP Psychiatric comorbidity: *NS* Medical Comorbidity *: PP>SCZ FHx: *NS* FHx-psychosis: *NS* Sensory Impairment: PP>SCZ	X scores on AMP syndromes of Paranoid-hallucinatory, Psycho-organic, Vegetative, Obsessive, Neurologic: *NS* X scores on AMP syndromes of Depressive, Manic, Apathic: SCZ>PP Presence of one FRS: *NS* No. of FRS: SCZ>PP		Use of neuroleptics and other Tx: *NS* Improvement at discharge: *NS*	Retrospective review of registry data. Age accounted for 22% of the variation in Dx *when controlled for age, differences were *NS* Multiple comparisons performed (risk of type I error). Majority of patients had received previous psychiatric treatment

Statistical significance is defined as an alpha level of 0.05 unless otherwise specified.   **statistics performed by author (AM) based on data presented in articl.e

Abbreviations

X = mean	ICD = International Classification of Diseases	G-K scale=Gittelman-Klein Premorbid Social Adjustment Scale
SD = standard deviation	DSM = Diagnostic Statistical Manual	BPRS=Brief Psychiatric Rating Scale
NS= not significant	SCZ = schizophrenia or schizophrenic psychosis	SAPS=Scale for the Assessment of Positive Symptoms
Dx = diagnosis/diagnostic	DD = delusional disorder	SANS=Scale for the Assessment of Negative Symptoms
FHx= family history of psychiatric illness	PP = paranoid psychoses	Ham-D=Hamilton Rating Scale for Depression
FHx-psychosis = family history of psychotic illness	w/ H = with non-prominent hallucinations	AIMS=Abnormal Involuntary Movement Scale
Sx = symptoms	w/o H = without hallucinations	NART=National Adult Reading Test
FRS=First Rank Symptoms	LP= late paraphrenia	PSE=Present State Examination
Tx = treatment	SCZA= schizoaffective disorder	SCID=Structured Clinical Interview for DSM-III-
DVA= Department of Veteran Affairs	AMP=Arbeitsgrmeinschaft fur Methodik und Dokumentation in der Psychiatrie	

Addressing the diagnostic uncertainty of late-onset psychotic disorder

The DSM-V working and study groups are addressing the problems with the current categorical system by considering "changes in criteria and adding new specifiers, subtypes, and diagnoses" (Kendler, Kupfer, Narrow, Phillips & Fawcett, 2009). Any change to the current diagnostic classification has to be supported by 1) a convincing argument that the proposed change would improve the reliability or validity of the diagnosis, and 2) new evidence that would support the change (Kendler et al., 2009). The approach taken by the DSM-V committee (Kendler et al., 2009) in the validation of diagnoses is a modification of the earlier proposed criteria by Kendler (1980), which consisted of three chronologically organized categories of validators: i) Antecedent: this includes familial aggregation and/or co-aggregration, socio-demographic and cultural factors, environmental risk factors and prior psychiatric history), ii) Concurrent: this includes cognitive, emotional, temperament and personality correlates, biological markers, patterns of comorbidity, and iii) Predictive: this includes diagnostic stability, course of illness and response to treatment. All of the predictive validators and the antecedent validator of familial aggregation and/or co-aggregation have been denoted "high priority" and thus, are given greater emphasis when deciding overall validity of a diagnosis (Kendler et al., 2009).

This approach is an adaptation of the highly influential, systematic approach for validating psychiatric illness first proposed by Robins and Guze (1970), which included the following criteria: clinical description, laboratory studies, specification of

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exclusionary criteria, follow-up studies to determine outcome, and studies of familial

aggregation. Updates to this approach have been recommended over the years, for

instance, to include the additional validators of molecular genetics and biology,

neurochemistry, neuroanatomy, neurophysiology, and cognitive neuroscience in order to

help link symptoms and diagnoses to their neural substrates (Andreasen, 1995). Kendell

and Jablensky (2003) have argued for a different model of validation that relies on the

existence of "zones of rarity", i.e., clear boundaries or qualitative differences, at the level

of the defining characteristic for the disease, whether this is at the syndromic level (as is

the case with most psychiatric disorders) or a more fundamental level such as genetics.

Kendell and Jablensky (2003) were quite aware that the consequence of defining

diagnostic validity in this manner was that most contemporary psychiatric disorders,

including schizophrenia, could not yet be described as valid disease categories. However,

they were quick to point out that validity did not preclude utility, and that many current

diagnostic categories in psychiatry have shown to be quite useful clinically as they yield

information about the likelihood of future recovery, relapse, deterioration, and

functioning (Kendell & Jablensky, 2003).

Study aims

The present study aims to characterize a large group of prospectively followed

patients with first episode late-onset psychotic disorder on key demographic, clinical,

treatment and prognostic variables. As one of the thorniest issues in the characterization

of these patients has been that of diagnostic classification, we also set out to examine

whether the currently nosological distinction of schizophrenia from delusional disorder, based on DSM-IV-TR criteria (APA, 2000) is valid or useful in patients with a late-onset primary psychosis. As part of this examination, we will explore whether clusters formed on the basis of select Brief Psychiatric Rating Scale items (BPRS; Overall & Gorham, 1962), which correspond to the "Criteria A" for both of the disorders, are consistent with our clinician-based diagnoses of schizophrenia and delusional disorder.

Hypothesis

Subjects from our prospective case series who have been categorized as having schizophrenia or delusional disorder using DSM-IV-TR criteria (APA, 2000) will fail to show any significant distinction based on the validity criteria proposed in the "Guidelines for Making Changes to the DSM-V" (Kendler et al., 2009).

Methods

Subjects

Subjects for this study were consecutively referred individuals who presented to the acute psychiatric service between the years of 1988 - 2009 with new onset psychosis after the age of 40. There also had to be an absence of 1) a formal past psychiatric history including prior contact with a psychiatrist, receiving a past psychiatric diagnosis, having a past psychiatric admission or receiving psychiatric treatment, 2) prior exposure to anti-psychotic, mood stabilizing or anti-depressant medication, 3) cognitive impairment or

dementia, 4) active substance abuse/dependence, and 5) a medical or neurological illness that could fully account for their presentation.

A total of 114 patients were initially referred. Five patients developed a manic episode early in the follow-up period and were removed from the series, leaving a total of 109 patients. Over the course of the study, a further 7 patients were excluded for the following reasons: 3 patients later revealed remote episodes of major depression; one patient had been diagnosed with a major neurological condition prior to presentation to our service; one patient was found to have cognitive impairment shortly after the time of presentation which was thought to account for the development of paranoia and two patients were found to have had recent cerebrovascular accidents once imaging was completed.

This left a total of 102 patients who met inclusion and exclusion criteria. At the time of presentation, 96 (93%) of the patients were admitted to an acute psychiatric ward while the remaining 6 patients were closely followed on an outpatient basis (i.e., twice-weekly for initial few weeks) by a staff psychiatrist and the research nurse. Patients received a diagnosis of a primary psychotic disorder variously termed: (late-onset) delusional disorder, (late-onset) schizophrenia, late-onset paranoid disorder and late paraphrenia. All were treated with low dose antipsychotic medication ± low dose benzodiazepine medication. The average daily neuroleptic dose was converted to chlorpromazine equivalents (Davis, 1974).

Clinical evaluation

At the time of presentation, basic demographic information and psychiatric, medical and social histories were elicited from patient interviews and collateral informants such as family members, friends and family physicians. The following was obtained: age at onset of psychotic symptoms, level of education, occupational and immigration history, marital status and history of offspring, whether a significant stress occurred just prior to symptom onset, and personal and family psychiatric histories. Significant medical and neurological conditions such as cardiovascular disease, head injuries, diabetes, thyroid dysfunction and seizure disorders were recorded. Patients were also assessed at the time of presentation for evidence of deterioration in self-care (e.g., disheveled appearance) and their ability, or lack thereof, to maintain their living quarters in a way that was out of keeping with their previous baseline. All patients had extensive medical and neuropsychiatric evaluations, which included physical and neurological examinations, laboratory investigations and neuroimaging studies, unless the patient refused. Patients were also screened for hearing and visual impairments unless they refused such assessments.

A series of rating scales was used to document signs and symptoms at baseline and following initiation of treatment, weekly for the first 4 weeks and at discharge by either a trained research nurse or psychiatrist (PR). For the patients (n = 6) who were managed as outpatients, "discharge" was defined as the end of the 4-week acute intensive monitoring period. The following rating scales were used: the Brief Psychiatric Rating

Scale (BPRS) (Overall & Gorham, 1962), the Global Assessment Scale (GAS) (Endicott, Spitzer, Fleiss & Cohen, 1976), the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959). Homicidality, which is not captured by any of the aforementioned rating scales, was specifically determined. Treatment response was assessed using the "response to treatment" variable that involved rating a patient's overall response on a 4-point scale: 0 = none (no perceptible change in symptomatology or function), 1 = full (non-symptomatic, complete return to previous baseline), 2 = partial (residual symptoms, has not returned to previous baseline functioning) and 3 = none, but patient refused/did not receive treatment. Response was also assessed by way of discharge scores on the BPRS, GAS, HAM-D and HAM-A.

Long-term follow-up

Patients were reassessed on an annual basis for diagnostic stability, frequency of relapse, independence or dependence with respect to living situation, the development of cognitive impairment or significant medical or neurological illness, and death. The diagnosis of dementia was made according to DSM-IV criteria. Patients' status on the latter four variables was determined at discharge, one year post-discharge and five years post-discharge.

Clarification of clinical diagnoses

Based on retrospective examination of patients' initial clinical chart and records, a senior psychiatry resident (AM) and staff psychiatrist (PR) reached consensus with respect to the re-classification of each patient in strict accordance with DSM-IV-TR (APA, 2000) diagnostic criteria as either having schizophrenia (SCZ, n=47) or delusional disorder (DD, n=55). This process specifically excluded reference to rating scales results.

Statistical Analyses

Statistical software

The computer program Statistical Package of the Social Sciences (SPSS™) Statistics GradPack 17.0 for Mac (SPSS Inc., Chicago, Illinois) was used to analyze the data.

Missing Data

Given that a small proportion (e.g., up to approximately 5%) of the data was determined to be missing for the vast majority of variables, a pair wise deletion analysis of missing data was performed (Norman & Streiner, 2008).

Sample characteristics

The group as a whole was characterized on a number of demographic, clinical, treatment and prognostic variables. Continuous variables with normal distributions are presented in terms of means and standard deviations (SD). For continuous variables with non-normal distributions, the median and interquartile ranges (IQR; 25th to 75th

percentile) are reported. The frequencies and percentages are provided for categorical variables.

Assessment of diagnostic validity: comparison of the DSM-IV-TR-based clinical diagnoses of delusional disorder (DD) and schizophrenia (SCZ)

The DSM-IV-TR-based diagnostic groups of DD and SCZ were compared based on the validators proposed in the "Guidelines for Making Changes to DSM-V" (Kendler et al., 2009). This included a comparison of (i) "Antecedent Validators" such as familial aggregation, socio-demographic and cultural factors and environmental risk factors; (ii) "Concurrent Validators" such as cognitive and emotional correlates, patterns of comorbidity and neural substrates by way of neuroimaging data; and (iii) "Predictive Validators" such as response to treatment, diagnostic stability and course of illness. We specifically assessed the following outcomes at one-year and five-years post-discharge: (i) transition from full independence to a supportive living arrangement; (ii) development of cognitive impairment; (iii) development of a neurological condition and (iv) death.

Certain validators were (i) not measured (e.g., temperament and personality correlates.); (ii) not applicable (e.g., formal psychiatric history which was an exclusion criterion) or (iii) not available (e.g., molecular genetics or other biological markers as they have not been established in this group of patients), and therefore were not included in the analysis. Functional measures such as the GAS and whether deterioration in

personal hygiene or living quarters was present (referred to hereon in as "deterioration") were included in the analysis. The mean and standard deviation of both groups (SCZ and DD) were calculated for the normally distributed continuous variables, which were compared using non-directional independent samples t-test statistics. The median and IQR were calculated for continuous variables with asymmetric distributions, which were compared using the non-parametric two-tailed Mann-Whitney U test. The categorical variables were compared using Pearson's chi-square statistics. The level of statistical significance was set at $p < 0.05$ for both continuous and categorical variables. In order to address the issue of multiple comparisons, a modification of the Bonferonni correction (Holm, 1979) was performed. The Holm-Bonferonni method maintains the experiment-wise error rate at 0.05 and is considered to be less conservative than the traditional Bonferonni correction (Norman & Streiner, 2008).

Exploring an independent data-driven approach to classification: BPRS-derived clusters

Using a k-means cluster analysis, patients were classified based on scores from select BPRS items at baseline. Although the BPRS has mainly been applied as an outcome measure to examine treatment efficacy, it has also been shown to be a time-efficient assessment instrument in facilitating differential diagnosis at acute inpatient admission (Hopko, Averill, Small, Greenlee & Varner, 2001). Cluster analysis is used to partition subjects into different groups on the basis of a minimal within-group and a maximal between-group variation (Steinley, 2006). We selected a 2-cluster solution (Cluster 1 and Cluster2) a priori in order to correspond with the two DSM-IV-TR-based

diagnostic groups (SCZ, DD). The eight selected BPRS items correspond to the "A"

criteria for SCZ and DD in the DSM-IV-TR and include: emotional withdrawal (item 3),

conceptual disorganization (item 4), mannerisms and posturing (item 7), suspiciousness

(item 11), hallucinatory behaviour (item 12), motor retardation (item 13), unusual thought

content (item 15) and blunted affect (item 16). The combination of the three symptom

construct of emotional withdrawal, motor retardation and blunted affect is highly

correlated with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen,

1983) and is the most widely used BPRS-based definition of negative symptoms

(Nicholson, Chapman & Neufeld, 1995). As per the BPRS, each item is scored on a 7-

point scale ranging from 1 (not present) to 7 (extremely severe). We then compared the

membership of the DSM-IV-TR-based groups of SCZ and DD to the BPRS-based

Clusters 1 and 2 using chi-square statistics.

Results

Sample characteristics

 The majority of the 102 patients in our series were females (60.8%) The group as

a whole had a mean age at presentation of 66.6 years (SD 11.74) and a mean age of onset

of 64.3 years (SD 12.0). The median duration of symptoms prior to presentation was 52

weeks (IQR: 16 to 104). All patients came from independent living situations. At the time

of presentation, the vast majority was either currently married (39.2%) or had been

married (19.6% divorced, 28.4% widowed), and had children (61.8%). This means over

80% had, at one time, been in a long-term relationship. Almost two-thirds of the patients

had not completed high school (61.8%) compared to 16.7% with post-graduate education in the form of vocational training, college or university. The majority of patients was employed or had previously worked (i.e., prior to retirement) full-time as either a professional, manager or business owner (29.4%) or as a labourer, clerk or homemaker (52.9%). Only 9.8% of patients had received social assistance or had a history of difficulty maintaining steady employment. One-third (33.3%) of patients were first generation immigrants to North America. None of the patients had a formal psychiatric history. Of the patients whose family psychiatric history was known (n=92; 90%), 41.3% had a first-degree relative with major psychiatric illness. This included 8.8% with a first-degree relative with a primary psychotic illness. In 40.2% of patients, a significant stress was determined to have occurred around the time of symptom onset, including, for example, death of a spouse or close relative or an experience that triggered memories of past traumas.

Medical co-morbidities were present in 66.7%. Conditions included hypertension, diabetes and heart, gastrointestinal or renal disease. 22.5% had hearing impairment and 2% had a serious visual impairment. Nearly one-fifth had a neurological history including headaches (n=7), a prior head injury (n=5), a seizure disorder (n=3) and one patient with a history of stroke that preceded the onset of psychosis by 7 years. Cobalamin levels were determined in 82.4% of patients at the time of presentation. 21.6% were found to be deficient (defined as a level of <145 pmol/L) and 33.3% had low-normal levels (defined as a level between 145 and 260 pmol/L) (Porter & Kaplan, 2010). Only

two-thirds (67.6%) of patients underwent cranial magnetic resonance imaging (MRI) at the time of presentation due to either patient refusal or the entry of some patients into the study prior to the widespread use of MRI scans in the clinical setting. Of the cranial MRI scans performed (n=69), 21.7% were normal; 18.8% had atrophy including two cases (2.9%) with ventricular enlargement; 52.2% had white matter lesions (WML) and/or silent infarct(s) (SI), and 4.3% had signs of both atrophy *and* WML and/or SI. The MRI of the patient with a remote history of stroke showed the old infarct but no new findings. A further 19 patients underwent CT scans of the brain: 42.1% were normal, 26.3% revealed silent infarct(s) and 31.6% had evidence of atrophy.

The frequency of "core" symptoms (e.g., positive symptoms, disorganization, negative symptoms) at baseline (n=102) are based on the subject scores on individual items of the BPRS. A symptom was reported as either being 'present' if score on BPRS was 2 (e.g., very mild) or above or 'not present' if score was 1 (see Table 2). As expected, the majority had positive symptoms (suspiciousness, hallucinatory behaviour or unusual thought content) and only a minority had negative symptoms (emotional withdrawal, motor retardation, blunted affect) or mannerisms and posturing . In terms of conceptual disorganization, when it was present (n=44, 43.1%) it was considered to be very mild (n=4, 9.1%), mild (n=15, 34.1%) or moderate (n=15, 34.1%) in the majority (77.3%) of cases.

Table 2. Frequency of individual symptoms		
	Present (%)	Not present (%)
Suspiciousness (BPRS item 11)	97 (95.1%)	5 (4.9%)

Hallucinatory behaviour (BPRS item 12)	73 (71.6%)	29 (28.4%)
Unusual thought content (BPRS item 15)	99 (97.1%)	3 (2.9%)
Conceptual disorganization (BPRS item 4)	44 (43.1%)	58 (56.9%)
Mannerisms and posturing (BPRS item 7)	14 (13.7%)	88 (86.3%)
Emotional withdrawal (BPRS item 3)	18 (17.6%)	84 (82.4%)
Motor retardation (BPRS item 13)	22 (21.6%)	80 (78.4%)
Blunted affect (BPRS item 16)	18 (17.6%)	84 (82.4%)

At the time of presentation, the mean BPRS score was 48.6 (SD 8.73), the mean HAM-D score was 16.2 (SD 7.41), the mean HAM-A was 12.1 (SD 6.59) and the median GAS was 30 (IQR: 21, 35). The majority (83.3%) did not show any evidence of significant deterioration in either their personal appearance/hygiene or in their living quarters. Three-quarters (75.5%) of the patients were found to have an absence of suicidality whereas 14.7% endorsed passive and 9.8% endorsed active suicidal ideation. Relatively more patients (32.2%) presented with homicidal ideation, active homicidal plans or recent history of aggressive acts.

For inpatients (n=96), the mean duration of hospitalization was 36.8 days (SD 20.75). For all patients, the median neuroleptic dose in CPZ equivalents was low at 133.5 mg (IQR: 93, 180). The response to treatment was as follows: 71.6% had a full response, 23.5% had partial response, 3.9% had no response, and 1% had no response in context of

treatment refusal. At discharge, the mean BPRS = 25.1 (SD 5.55), the mean GAS = 68.6 (SD 9.52), the mean HAM-D = 4.16 (3.84) and the median HAM-A = 11.5 (IQR: 7, 16).

At the time of discharge, 13 (12.7%) transitioned from living independently prior to their presentation to a form of supportive living accommodation. During the acute period of hospitalization, one patient suffered a cerebrovascular accident and developed subsequent mild cognitive impairment, one patient was found to have cancer and two patients were diagnosed with other medical issues. Three patients were found to have evidence of mild cognitive impairment at discharge, including the patient who developed cognitive impairment post-stroke. No deaths occurred during hospitalization or, for those who were not admitted to hospital, the acute monitoring period.

The mean duration of follow-up post-discharge was 5.6 years (SD 4.67) with a range 0 to 18 years. A total of 84 (81.3%) patients were followed for at least one year subsequent to their discharge. Reasons for patients being lost to follow-up include the patient moving or being lost to contact. Of the 84 patients who were followed for one year or more, 46 (54.8%) had at least one relapse with the cause being attributed to medication non-adherence in 78.3% of the cases. None of the patients went on to develop a major affective illness or other diagnosis that could have accounted for their psychosis, during the follow-up period.

At one-year post-discharge (n = 84), 19 (22.1%) patients were living in a type of supportive housing arrangement. Four patients had experienced a cerebrovascular accident, one patient was diagnosed with breast cancer and one patient developed normal pressure hydrocephalus requiring a shunt, the complications of which were thought to have contributed to this patient's death – the only known death at one-year follow-up. Three (3.5%) showed signs of mild cognitive impairment (including one patient who had mild cognitive impairment at discharge) and 14 (16.3%) patients were diagnosed with dementia (including two of the patients who had mild cognitive impairment at discharge).

At five-years post-discharge (n = 67), a total of 27 patients (40.3%) had transitioned to a supportive living arrangement and 21 (31.3%) patients had been diagnosed with dementia. A total of 14 (20.9%) patients had developed some form of neurological condition including stroke, multiple sclerosis and Parkinson's disease, whereas 8 (11.9%) patients had been diagnosed with other significant medical complications and a total of 13 (19.4%) patients had died.

Assessment of diagnostic validity: comparison of the DSM-IV-TR-based clinical diagnoses of schizophrenia (SCZ) and delusional Disorder (DD)

Antecedent validators

Tables 3 and 4 provide the results of the comparison between groups on the various antecedent validators. There were no significant differences between the SCZ and DD groups on age at presentation or age at onset, sex ratio, educational or

occupational histories, current marital status, whether they had children or whether a

significant stress preceded the onset of symptoms. There was a non-significant trend for

DD patients to have a history of immigration (41.8%) compared to SCZ patients (23.9%).

There were no significant differences between groups on family psychiatric history.

Table 3. Socio-demographic and environmental risk factors				
Variable	**SCZ (*n*=47)**	**DD (*n*=55)**	**Statistic (df)**	***P***
Mean age at presentation (SD) (years)	67.1 (12.43)	66.1 (11.22)	$t(100)=0.40$	0.69
Age at onset (SD) (years)	64.6 (12.38)	64.1 (11.71)	$t(100)=0.19$	0.85
Sex (M:F)	14:33	26:29	$\chi^2(1)=3.25$	0.07
Education Level				
Did not complete secondary school	29	34	$\chi^2(2)=0.03$	0.99
Secondary school	8	10		
Post-secondary	8	9		
Data not available	2	2		
Marital Status				
Single/Never Married	4	9	$\chi^2(3)=4.71$	0.19
Married/Common-Law	17	23		
Divorced	8	12		
Widowed	18	11		
Employment History				
Professional/Business owner/Manager	16	14	$\chi^2(2)=2.01$	0.37
Labourer/Clerical/ Homemaker	22	32		
Welfare/Disability/Un-employed	6	4		
Data not available	3	5		
Immigration History				
Non-immigrant	35	32	$\chi^2(1)=3.60$	0.06
Immigrant	11	23		
Children				
None	14	25	$\chi^2(1)=2.63$	0.11
Yes	33	30		
Precipitant stress				

None identified	31	30	$\chi^2(2)=1.69$	0.43
Yes	16	25		

Table 4. Family psychiatric history				
Variable	**SCZ**	**DD**	**Statistic (df)**	***P***
FDR with psychiatric history				
None	24	30	$\chi^2(1)=0.60$	0.44
Present	20	18		
Not known	3	7		
FDR with primary psychosis				
None	38	45	$\chi^2(1)=1.42$	0.23
Present	6	3		
Not known	3	7		

FDR = First Degree Relative

Concurrent validators

Tables 5, 6 and 7 report the presence of co-morbidity, neuroimaging results and the symptom/functional correlates at presentation, respectively. There was a statistically significant, but clinically trivial, difference between mean BPRS scores at baseline, with those in the SCZ group having a higher score (mean difference = 3.70 with a 95% confidence interval (CI) of 0.32 to 7.08). Similarly, the SCZ group had a significantly higher, but not clinically meaningful difference on the median GAS score at baseline (see Figure 1). No differences were detected between groups on HAM-D or HAM-A scores, on the presence of either suicidality or homicidality, or on the measure of deterioration. The SCZ and DD patients did not differ in neuroimaging outcomes or on the presence of co-morbid medical illness, hearing and visual impairments or vitamin B12 deficiency.

Table 5. Comorbidities

Variable	SCZ (n=47)	DD (n=55)	Statistic (df)	*P*
Significant Medical History				
No	13	21	$\chi^2(1)=1.26$	0.26
Yes	34	34		
Hearing Impairment				
None	34	45	$\chi^2(1)=1.30$	0.25
Present	13	10		
Visual Impairment				
None	46	54	$\chi^2(1)=0.013$	0.91
Present	1	1		
Vitamin B12 level				
Deficient: 0–144 pmol/L)	11	11		
Low normal: 145–260 pmol/L	18	16	$\chi^2(2)= 0.26$	0. 88
Above 261 pmol/L	13	15		
Data unavailable	5	11		

Table 6. Neuroimaging				
Variable	SCZ	DD	Statistic (df)	*P*
MRI results				
Normal	6	9		
Atrophy	5	8		
WML and/or SI	19	19	$\chi^2(3)=1.27$	0.74
Atrophy and WML/SI	2	1		
Data unavailable	15	20		

Table 7. Symptom and functional correlates				
Variable	SCZ (*n*=47)	DD (*n*=55)	Statistic (df)	*P*
Mean BPRS at presentation (SD)	50.6 (8.50)	46.9 (8.64)	t(100)=2.17	0.03
Median GAS at presentation (IQR)	25 (21-30)	30 (25-40)	U= 940.00 Z = -2.39	0.02
Median HAM-D at presentation	0 (0-3)	1 (0-4)	U= 1170.50 Z = -0.87	0.39
Median HAM-A at presentation (IQR)	12 (8-16)*	11 (6-16)	U= 1115.00 Z = -0.61	0.54
Deterioration at baseline				
No	37	48	$\chi^2(1)=1.33$	0.25

Yes	10	7		
Suicidality at baseline				
None	37	40	$\chi^2(2)=1.16$	0.56
Passive	5	10		
Active	5	5		
Homicidality at baseline				
None	31	38	$\chi^2(2)=1.76$	0.42
Passive	10	14		
Active	6	3		

*n=45

Predictive validators

Table 8 presents the data corresponding to treatment and treatment response. There was no difference between the ratio of outpatients to inpatients between the SCZ and DD groups. However, inpatients classified as having SCZ tended to have longer admission stays compared to DD. The median daily neuroleptic dose in chlorpromazine equivalents did not significantly differ between the groups and SCZ and DD patients did not differ on their response to treatment or on the BPRS, GAS or HAM-A scores at discharge. A statistically, but not clinically, significant difference was detected between groups on the median HAM-D at discharge. Table 9 reports on the median duration of follow-up as well as rate of relapses per for all patients for whom relapse data was available for. No differences between groups were detected on either variable.

Table 8. Treatment and response to treatment				
Variable	**SCZ (*n*=47)**	**DD (*n*=55)**	**Statistic (df)**	***P***
Inpatient admission				
No	2	4	$\chi^2(1)=0.42$	0.68
Yes	45	51		
Median duration of inpatient	33 (25-57.5)	30 (21-40)	U=865.50	0.04

			Z=-2.07	
admission (days) (IQR)			Z=-2.07	
Median neuroleptic dose CPZ equivalent (mg) (IQR)	150 (100-200)	125 (75-165)	U=1133.00 Z=-1.07	0.28
Response to treatment				
None	2	2	$\chi^2(2)=0.31$	0.86
Full	35	38		
Partial	10	14		
Refused treatment	0	1		
Median BPRS at discharge (IQR)	23 (21-29)	25 (22-28)	U=1205.00 Z=-0.59	0.56
Median GAS at discharge (IQR)	70 (61-75)	70 (61-75)	U=1258.00 Z=-0.23	0.82
Median HAM-D at discharge (IQR)	1 (0-3)	1.5 (0-3)*	U=745.50 Z=-2.46	0.01
Median HAM-A at discharge (IQR)	1 (0-3)	1.5 (0-3)**	U=1217.00 Z=-0.36	0.72

*n=53

**n=54

Table 9. Duration of follow-up and relapse rate				
Variable	**SCZ** **(n= 47)**	**DD** **(n= 55)**	**Statistic (df)**	***P***
Median duration of follow-up (IQR) (years)	5 (2-8)	5 (1-9)	U=1072.00 Z=-1.49	0.14
Mean number of relapses per year (SD)	0.15 (0.20)*	0.24 (0.33)**	t(83)=-1.39	0.17

*n=41

** n=44

Tables 10 and 11 summarize the outcomes (lost to follow-up, transition to supportive living arrangement, development of cognitive impairment, development of neurological condition and death) within one-year and five-years post discharge. The data for patients who have yet to receive a follow-up assessment due to their more recent enrollment in the study is recorded as "incomplete", as is when the outcome (e.g., development of neurological condition) is not known due to inability to ascertain their

cause of death. No differences on any of the outcomes were found between the SCZ and

DD diagnostic groups.

Table 10. Status within 1-year post-discharge				
Variable	**SCZ (n=47)**	**DD (n=55)**	**Statistic (df)**	*P*
Lost to follow-up				
No	42	43	$\chi^2(1)=1.23$	0.27
Yes	5	10		
Incomplete data	0	1		
Move to supported living accommodations				
No	31	36	$\chi^2(1)=0.80$	0.37
Yes	11	8		
Lost to follow-up/Incomplete data	5	11		
Development of cognitive impairment				
No	34	35		
Mild	1	2	$\chi^2(2)=0.30$	0.86
Dementia	7	7		
Lost to follow-up/Incomplete data	5	11		
Development of neurological illness				
No	39	41	$\chi^2(1)=0.003$	0.95
Yes	3	3		
Lost to follow-up/Incomplete data	5	11		
Death				
No	42	42	$\chi^2(1)=0.97$	0.33
Yes	0	1		
Lost to follow-up/Incomplete data	5	11		

Table 11. Status within 5-years post-discharge				
Variable	**SCZ (n=47)**	**DD**	**Statistic (df)**	*P*

		(n=55)		
Lost to follow-up				
No	34	33	$\chi^2(1)=2.58$	0.11
Yes	8	17		
Incomplete data	5	5		
Move to supported living accommodations				
No	20	20	$\chi^2(1)=0.02$	0.88
Yes	14	13		
Lost to follow-up/Incomplete data	13	22		
Development of cognitive impairment				
No	22	21		
Mild	1	2	$\chi^2(2)=0.39$	0.82
Dementia	10	11		
Lost to follow-up/Incomplete data	13	22		
Development of neurological illness				
No	28	22	$\chi^2(1)=1.18$	0.28
Yes	6	9		
Lost to follow-up/Incomplete data	13	24		
Death				
No	29	25	$\chi^2(1)=0.97$	0.32
Yes	5	8		
Lost to follow-up/Incomplete data	13	22		

None of the comparisons remained statistically significant using the Holm-Bonferonni method to correct for the multiple tests performed.

An independent data-driven approach to classification: BPRS-derived clusters

The results of the k-means cluster analysis are presented in Table 12. The BPRS items corresponding to conceptual disorganization, mannerisms and posturing, and

negative symptoms significantly (p ≤ 0.001) contributed to cluster membership. Cluster 1

(n= 91) was characterized by no (1) to very mild (2) levels of negative symptoms and

disorganization (i.e., conceptual disorganization and/or mannerisms and posturing items),

whereas Cluster 2 (n=11) was characterized by mild (3) to moderately severe (5) levels of

items corresponding to negative symptoms and disorganization. The severity of

hallucinatory behaviour, unusual thought content and suspiciousness items were not

found to be significantly discriminating in the 2-cluster solution. Our DSM-IV-TR-based

diagnostic groups (SCZ, DD) did not correspond to the BPRS-based clusters: Cluster 1

had 40 SCZ and 51 DD while Cluster 2 had 7 SCZ and 4 DD. There was no significant

difference between SCZ and DD in terms of cluster membership (χ^2(1)=0.22, p=0.34).

Table 12. Final cluster centres based on select BPRS items								
	Emotional withdrawal	Conceptual disorganization	Mannerisms and posturing	Suspiciousness	Hallucinatory behaviour	Motor retardation	Unusual thought content	Blunted affect
Cluster 1 (89.2%) (n=91)	1	2	1	6	4	1	5	1
Cluster 2 (10.8%) (n=11)	5	4	3	5	4	3	5	3
F (df=1)	376.34	11.29	40.50	2.38	0.10	28.32	0.23	33.81
p	**<0.001**	**0.001**	**<0.001**	0.13	0.75	**<0.001**	0.63	**<0.001**

Discussion

This series represents the largest reported to date, of first-episode prospectively

studied late-onset primary psychotic disorder patients. The first objective of the study

was to characterize the group as a whole on a number of demographic, clinical, treatment and outcome variables and to determine if findings reported in the literature on smaller and/or or retrospective studies are supported. The second objective, and the main research question, was to assess whether there is validity or utility to maintaining the DSM-IV-TR distinctions between schizophrenia (SCZ) and delusional disorder (DD) when diagnosing patients who first develop a primary, non-affective disorder in mid to late life. The third and final objective was to explore whether independent data-driven clusters, formed using select items from the Brief Psychiatric Rating Scale corresponding to the "Criteria A" of schizophrenia and delusional disorder would be consistent with the DSM-IV-TR clinician based diagnostic groups of SCZ and DD.

Late-onset psychotic disorder group characteristics

In keeping with previous reports (as reviewed by Howard et al., 2000), our patient group consisted of a greater number of women than men (1.8:1). All of our patients lived independently prior to presentation and the majority had been married with children and had an intact work history either outside or inside the home in keeping with other studies which found this group to have superior premorbid psychosocial functioning compared to early-onset schizophrenia patients (Castle et al., 1997; Jeste et al., 1997, Vahia et al., 2010). In our series, the average age at presentation was 66.6 years and the average age of onset was 64.3 years consistent with the designation of "very-late-onset" suggested by Howard et al. in 2000. Notably, the median duration between onset of symptoms and presentation to acute services was one year. In terms of potential risk factors,

approximately 40% of patients had experienced an identifiable stressful life event around the time of onset of symptoms and one-third of patients were immigrants, the latter finding in keeping with results of previous studies (Reeves et al., 2001; Mitter et al., 2004) which found a higher incidence of very-late-onset schizophrenia-like psychosis in African and Caribbean immigrants to the United Kingdom compared to British-born peers. There has been accumulating evidence to suggest that psychosocial stressors such as migration, childhood trauma and adverse life events, particularly with cumulative exposure, increase the risk of developing psychosis through a possible underlying mechanism of "behavioural sensitization" in which exposures lead to increased behavioural (e.g., emotional or psychotic reactions to stress) and biological (e.g., dysregulation of the hypothalamus-pituitary-adrenal axis and dopamine pathways) responses (van Winkle, Stefanis & Myin-Germeys, 2008). Forty-one percent had a first-degree relative with a psychiatric problem, a similar number found in an earlier study (Almeida et al., 1995b), although intermediate between other reports of 65-88% (Girard & Simard, 2008) and 22% (Brodaty et al., 1999). In our series, approximately 9% had a first degree relative with a primary psychotic illness, falling within the 2.3 – 16.7 % range reported by others for comparable patient populations. (Pearlson et al., 1989; Howard et al., 1997; Hasset, 1999; Brodaty et al., 1999; Girard & Simard, 2008).

At the time of presentation, two-thirds of our patients had a significant medical history and one-fifth had a significant neurological history, perhaps not surprising given the older age of patients. There is a notable dearth of information on the relationship

between medical and neurological comorbidity and the broader diagnostic group of patients with late-onset psychotic disorder, possibly due to the fact that by definition the psychosis cannot be assessed as being secondary to a medical/neurological condition. In reality, this is a rather crude assessment that is susceptible to change over time with increasing knowledge of how systemic medical conditions, such as inflammatory, endocrine and cardiovascular disorders affect brain function. However, it is noted that Sachdev et al. (1999) found no differences between patients with late-onset schizophrenia (onset over age 50), older patients who had developed schizophrenia earlier in life and healthy age-matched controls, on rates of hypertension, coronary artery disease, cerebrovascular disease, diabetes or peripheral vascular disease. Similarly, Tonkonogy and Geller (1999) reported no differences in hypertension or diabetes between late-onset paranoid psychosis and early-onset schizophrenia cases. Particularly noteworthy is our novel finding of vitamin B12 deficiency in one-fifth of the cases and a low-normal level in one-third of cases. Case reports and studies have attributed psychosis to vitamin B12 deficiency and have demonstrated a resolution of psychosis with vitamin B12 supplementation only (as reviewed by Hutto, 1997). Furthermore, recent evidence has demonstrated that vitamin B12 deficiency is associated with increased rates of brain atrophy and cognitive decline in the general elderly population (Vogiatzoglou et al., 2009; Tangney, Tang, Evans & Morris, 2009). For ethical reasons, patients with vitamin B12 deficiency in the current study received both antipsychotic medication and vitamin B12 supplementation, thereby making it difficult to assess the association between correction of the deficiency and recovery status. The association between vitamin B12 deficiency

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and the development of psychosis in late life requires further attention, particularly given prevalence and treatability of such a deficiency in older adults. Our finding that 22.5% of patients had a hearing impairment is consistent with the 22.9% reported in a descriptive study of patients over age 60 with late-onset psychotic disorder Hassett (1999). This author noted that the rate is similar to that in the general elderly population. Overall, a fairly wide range of hearing impairment has been reported for this group, from 17% to 40.7% (Almeida et al. 1995b; Prager & Jeste, 1993; Pearlson et al., 1989; Brodaty et al., 1989) likely due to differences in its assessment.

Approximately 80% and 60% of cases that underwent an MRI or CT scan, respectively, had some degree of an abnormal finding (e.g., atrophy, white matter lesions, silent infarct). However, the significance of these findings are unclear as previous studies attempting to link these potential degenerative anatomic correlates to late-onset psychotic disorder have yielded conflicting results (Pearlson, 1999). Although white matter lesions and cortical atrophy are found commonly in healthy elderly patients, there is emerging evidence that they are, in fact, associated with progressive cognitive decline (Kramer et al., 2007). It has long been known that pathology of the white matter tracts of the brain results in a functional disconnection between those parts of the nervous system that communicate through the affected areas, leading to corresponding clinical consequences depending upon the location of the white matter pathology (Rosebush, Anglin & Mazurek, 2009). Therefore, studies focused upon careful attention to the precise location

of WMH and their correlation with symptoms may advance our understanding of their underlying biology of particular disorders such as late-onset psychotic disorder.

As would be expected based on our definition of late-onset psychotic disorder, 97.1% of our cases had delusions and 71.6% had hallucinations. However, these rates of delusions and hallucination are also in keeping with the high rates seen in late-onset schizophrenia patients (Pearlson et al., 1989), the diagnostic criteria of which does not require either symptom to be present. Similar to previous studies of those who develop a primary, non-affective psychosis later in life, only a minority of the patients in this study demonstrated negative symptoms such as affective blunting or features of catatonia (e.g., abnormal mannerisms and posturing) more typical of early onset schizophrenia (Pearlson et al., 1989; Howard et al., 1993; Castle et al., 1997; Brodaty et al., 1999; Sato et al., 2004). The overall prevalence of conceptual disorganization was notably higher in our study (43%) than what has been previously cited for formal thought disorder (e.g., Pearlson et al., 1989; Howard et al., 1993; Castle et al., 1997). This is likely due to the fact that the majority of the cases were of mild-moderate in severity and therefore, may have not been identified in these other studies. At the time of presentation, the mean BPRS score was 48.6 (SD 8.73), which has been found to correspond to a "moderately ill" level of symptomatology on the Clinical Global Impression Scale (Leucht et al., 2005) in schizophrenia patients during acute exacerbations. This BPRS score was higher than the mean BPRS score of 32.9 (SD 7.6) reported in a cross-sectional sample of late-onset schizophrenia (Jeste et al., 1995), although this study recruited from a variety of

care-settings and therefore may not reflect the current sample who were presenting to an acute hospital care service. The mean HAM-D score at presentation was 16.2 (SD 7.41), corresponding to "mildly depressed" and falling just below the typical cut-off for admission into depression studies (Endicott, Cohen, Nee, Fleiss & Sarantakos, 1981). Interestingly, even in the instance of higher HAM-D scores, patients did not require antidepressant treatment for their HAM-D scores to significantly improve – an observation that further delineates this group from a primary depressive illness with psychotic features. The median GAS score at presentation was 30 (IQR: 21, 35), consistent with behavior that is considerably influenced by either delusions *or* hallucinations, a serious impairment in communication *or* an inability to function in almost all areas (Endicott et al., 1976). This score was essentially the same as the mean GAF score of 32.7 (11.3) of neuroleptic-naïve late-onset schizophrenia patients at the time of hospital admission (Sato et al., 2004) and the 'worse' mean GAF score of 27.8 (SD 9.3) recorded in another study of late-onset schizophrenia patients (Brodaty et al., 1999). Given that the majority of cases (83.3%) did not show any evidence of significant deterioration in either their personal appearance/hygiene or in their living quarters, the median score on the GAS (a tool that considers both symptom severity and functioning and is designed to reflect whatever is most severe of these two domains), appears to have more likely captured the severity of symptoms rather than level of functioning. A minority of patients were found to be suicidal or homicidal consistent with the only other study known to report specifically on these symptoms (Yassa & Suranyi-Cadotte, 1993). The ideation associated with these features was always associated with the delusional

thought content. A full response rate of 71.6% was not much higher than the 48-61% rate previously reported (Howard et al., 2000) for comparable patient groups. The mean BPRS at discharge of 25.1 (SD 5.55) corresponds to being "mildly ill" on the Clinical Global Impression Scale (Leucht et al., 2005). The low median neuroleptic dose of 133.5 mg (CPZ equivalents) was consistent with that observed in other studies (e.g., Brodaty et al., 1999; Vahia et al., 2010).

As previously discussed, there is relatively limited information regarding the longitudinal course of illness for patients with late-onset psychotic disorder given the lack of prospective longitudinal studies. In our series, approximately half of all patients followed for more than a year experienced a relapse and in almost every case this was attributed to antipsychotic medication non-compliance or a medically supervised tapering of medication after a long period of stability. Based upon this, it is likely that patients with late-onset psychotic disorder, like those who develop schizophrenia earlier in life, require long-term treatment with antipsychotic agents. By five-years post-discharge, 31.3% had been diagnosed with dementia. Other studies have reported similar proportions (i.e., 26% and 28%) of patients who went on to develop dementia during a 5 year (Brodaty et al., 2003) and up to a 10-year (Leinonen et al., 2004) follow-up period. Rabins and Lavrisha (2003) reported that approximately 50% of individuals with late-onset schizophrenia (age of onset over 45 years) had dementia at 10 years, which was noted to be higher than the expected 10-year incidence rate of approximately 20%.

Despite the confusion brought on by the various terms, concepts, diagnostic criteria and age-cut-offs used to define and describe late-onset psychosis in the research and clinical realms over the last century, a remarkably uniform picture has emerged with respect to its demographic, pre-morbid, clinical, neurocognitive, treatment and prognostic features. Inconsistencies between studies have been typically due to differences in, and limitations of, the methodologies used. The characterization of our large series of prospectively followed late-onset psychotic disorder patients not only strengthens what is already known about this presentation to date, but also sheds new light in terms of the longitudinal course of illness, the improvement of associated depressive symptoms with antipsychotic treatment alone, and the possible roles that vitamin B12 deficiency and stressful life events may play in its development.

Is there validity and/or utililty in distinguishing schizophrenia and delusional disorder in the late-onset population?

Late-onset psychotic disorder patients can be classified as either having schizophrenia or delusional disorder using current diagnostic criteria (Quintal et al., 1991; Almeida et al., 1995a). However, the validity and utility of such a distinction in late-onset patients has not been entirely clear (Jørgensen & Munk-Jørgensen, 1985; Quintal et al., 1991; Howard et al., 1994a; Almeida et al., 1995a; Evans et al., 1996; Roth & Kay, 1998; Riecher-Rössler et al., 2003). Previous work, supported by the current study, have shown that whereas the majority of late-onset psychosis cases have both delusions and hallucinations, only a relatively minority have the negative symptoms, catatonia or significant thought disorganization that, apart from hallucinations and delusions, make up

the diagnostic criteria for schizophrenia. Therefore, the distinction between making a diagnosis of schizophrenia over delusional disorder typically rests on whether the delusions are bizarre or not and/or whether the hallucinations are prominent or not. However, a recent critical review of the literature has shown that the notion of 'bizarreness' lacks reliability and validity evidence, leading these authors to recommend that the presence of bizarre delusions should no longer be considered sufficient for "Criteria A" for schizophrenia to be met (Cermolacce et al., 2010). Fortunately, the DSM-V working group is in agreement and have recently recommended the elimination of the requirement that only one "characteristic" symptom, such as bizarre delusions, needs to be present for a diagnosis of schizophrenia to be made (APA, 2011a). Furthermore, it appears that the DSM-V working group is also proposing to eliminate the requirement that delusions are "non-bizarre" in the diagnostic criteria of delusional disorder and instead will include a "bizarre" specifier (APA, 2011b).

Using the diagnostic validation approach described in the "Guidelines for Making Changes to DSM-V" (Kendler et al., 2009) with our prospectively studied case series of 102 late-onset psychotic disorder patients classified as either having SCZ (n=47) or DD (n=55), we have shown a compelling lack of evidence supporting the distinction of these two diagnostic groups. In fact, given the multiple comparisons performed in our study, we would expect a small number of comparisons to be significant on the basis of chance alone. When the Holm-Bonferroni correction is applied to address the multiple tests performed, none of the comparisons remained statically significant.

Of the antecedent validators tested, there were no statistically significant differences between the SCZ and DD groups even prior to the Holm-Bonferroni correction. This includes the "high priority" validator of familial aggregation, which is given greater emphasis when deciding overall validity of a diagnosis (Kendler et al., 2009). These findings are consistent with previous findings of non-significance between diagnostic groups on a range of demographic variables (Flint et al., 1991; Yassa & Suranyi-Cadotte, 1993; Howard et al., 1994a; Evans et al., 1996), lifetime stressors (Riecher-Rössler et al., 2003), psychiatric comorbidity (Riecher-Rössler et al., 2003), premorbid functioning (Evans et al., 1996) and familial aggregation (Evans at al., 1996; Riecher-Rössler et al., 2003). There was a trend (p = 0.06) towards DD patients more likely being immigrants than SCZ patients. Migration has been well established as risk factor for the development of non-affective psychotic disorders, as a group, in both first-generation and second-generation immigrants (Bourque, van der Ven & Malla, 2010). The only known study to directly compare schizophrenia and delusion disorder (of any age of onset) on immigration status found an increased risk in the latter group (Kendler, 1982). However, this study was limited methodologically and compared the two groups using data and non-standardized diagnostic criteria derived from the early part of the 20th century (Kendler, 1982).

In terms of concurrent validators, no difference was detected between SCZ and DD groups on a number of symptom correlates. Previous studies have also failed to show

any major differences in symptomatology (Flint et al., 1991; Yassa & Suranyi-Cadotte, 1993; Howard et al., 1994a; Evans et al., 1996; Riecher-Rössler et al., 2003), on neuropsychological measures (Evans et al., 1996) or on the presence of suicidality or homicidality (Yassa & Suranyi-Cadotte, 1993) between groups. Similar to earlier work (Yassa & Suranyi-Cadotte, 1993), our SCZ and DD groups also did not differ on the presence of hearing or visual sensory deficits. The SCZ group was found to have a statistically significantly higher mean BPRS score (p=0.03) and a lower median GAS score at presentation compared to the DD group (p=0.02). However, the small mean difference of 3.76 (95% CI of 0.37 to 7.14) detected between the two groups on the BPRS, a scale that ranges from minimum score of 18 to a maximum score of 126, is not thought to be clinically relevant. Leucht et al. (2006) found that an absolute change of at least 10 on the BPRS corresponded roughly to a "minimal improvement" according to clinical judgement and to a change in one severity step on the Clinical Global Impression Scale. Furthermore, when the item corresponding to severity of hallucinations (one of the two key criteria in making the distinction between SCZ and DD diagnostic criteria) was removed from the BPRS total score at presentation, the difference no longer remained (U=1189.50, Z=-0.69, P=0.49). In terms of the difference detected on the GAS, the actual median difference of 5 points on the GAS (see Figure 1), a scale that is divided into 10-point intervals, which clinicians typically score on the deciles or mid-deciles (Aas, 2010), is also arguably not in keeping with a clinically significant difference between groups. However, it does appear that the DD group did have a greater spread over less severe scores. Given scores on the GAS are based on both function level and symptomatology

severity, it may reflect the fact that DD patients have less (or no) hallucinations by definition. Notably, there was no significant difference detected between groups in terms of presence of deterioration in personal care.

Figure 1. Boxplots of GAS at presentation by group
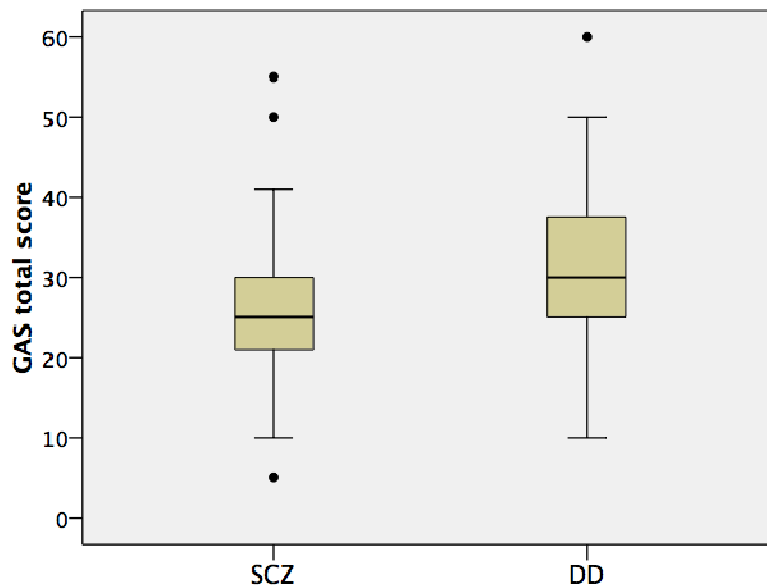
In terms of predictive validators, all of which were earmarked as "high priority" by the Guidelines for Making Changes to DSM-V (Kendler et al., 2009), no differences were detected between the DD and SCZ groups with respect to neuroleptic treatment, response to treatment, course of illness (e.g., relapse rate) or diagnostic stability (e.g., development of dementia). Again, these results are consistent with previous research that did not find differences in neuroleptic use (Flint et al., 1991; Evans et al., 1996; Riecher-Rössler et al., 2003), response to medication (Howard et al., 1994a) or improvement at time of discharge (Riecher-Rössler et al., 2003), stability over longer follow-up period (Yassa & Suranyi-Cadotte, 1993) or stability of initial diagnosis (Evans et al., 1996).

Furthermore, with respect to diagnostic stability, none of the patients in the currents series were known to develop an affective illness during follow-up. Statistical differences (in the absence of the Holm-Bonferroni correction) were found between the two groups on median duration of first inpatient admission (p=0.04) (see Figure 2) and median HAM-D at discharge (p=0.01) (see Figure 3). The medians for duration of first inpatients admission for the SCZ and DD groups were essentially the same, 33 and 30 days, respectively. However, as Figure 2 depicts the difference between groups is in the variability of duration, with the SCZ group having more individuals with longer length of stay. Although this result does not point to a clinically relevant difference between groups, it potentially points to a 'spectrum of severity' with longer duration of hospitalization a marker for severity or for treatment resistance. Similarly, a statistically significant difference was detected between groups on the median HAM-D at discharge, although the median and IQR values were essentially the same between groups (see Figure 3). Of note, the outlier in the SCZ group had relatively lower HAM-D scores at presentation and throughout admission, and was only observed to have a significant increase in score in anticipation of discharge. Importantly, the majority of patients (as per the IQRs) in both groups had scores in the normal range upon discharge.

Figure 2. Boxplots of the Duration of First Inpatient Admission by group
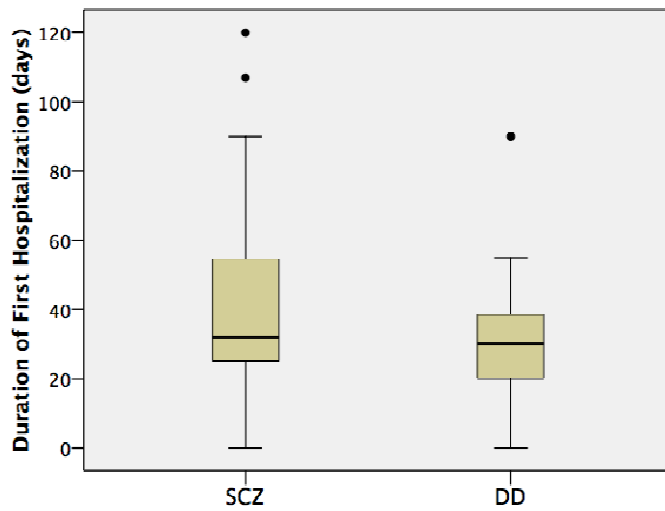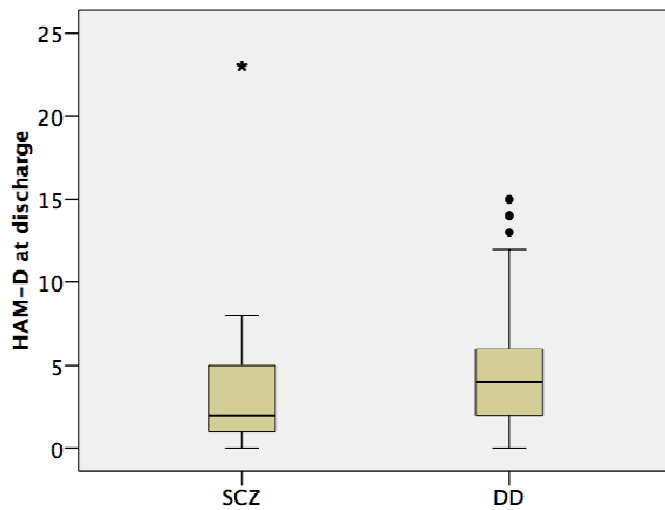
Figure 3. Boxplots of HAM-D total scores at discharge by group

The validity in distinguishing between schizophrenia and delusional disorder in the late-onset population has been called into question by previous researchers (Jørgensen & Munk-Jørgensen, 1985; Howard et al., 1994a; Riecher-Rössler et al., 2003). The results from the current study, the largest known first-episode prospectively studied case series

of late-onset psychotic disorder, confirms the lack of any appreciable difference on a variety of antecedent, concurrent and predictive validators. In regards to the concept of utility (Kendell & Jablensky, 2003), the diagnostic groups of schizophrenia and delusional disorder failed to show clinical usefulness in terms of being distinct in the likelihood of future recovery, relapse, deterioration and functioning. Furthermore, dividing the late-onset psychotic disorder group into these sub-groups carries the real risk of reducing our ability to identify and recruit a sufficient number of cases for study purposes.

Exploration of an independent data-driven approach to classification

Our attempt to use a data-driven approach to classification based on select BPRS item scores that correspond to "Criteria A" for schizophrenia and delusional disorder in the DSM-IV-TR highlighted the scarcity of negative symptoms, catatonia and thought disorganization in the patient group overall. Not unexpectedly, it was the presence of the BPRS items corresponding to these particular symptoms that were significant in discriminating the two clusters – a small group who was characterized by mild to moderate levels of these symptoms and a much larger group who essentially did not have these symptoms. These clusters did not correspond to the clinician-derived diagnostic groups of schizophrenia and delusional disorder based on DSM-IV-TR criteria. This may be due to the fact that in several cases, the clinical-based classification rested upon whether the patients' hallucinations were prominent or not and/or whether their delusions were bizarre or non-bizarre. The severity ratings of these BPRS items (i.e., hallucinatory

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behaviour and unusual thought content) are unlikely to capture such distinctions. Our

analysis reveals the difficulty in separating patients with late-onset psychotic disorder into

diagnostic subtypes on the basis of individual psychotic symptoms alone. Previous studies

have also attempted to subtype late-onset psychotic disorder based on clinical

presentation with limited success (Kay & Roth, 1961; Post, 1966; Holden, 1987; Howard

et al., 1994a). Howard et al. (1994a) reported a poor association between their cluster

groups based on clinical and demographic features, and the ICD-10 clinical diagnoses of

schizophrenia and persistent delusional disorder. Furthermore, clusters did not correspond

to the clinical subtypes derived by earlier authors (Howard et al., 1994a).

Study Limitations

The current study lacked a comparator group (e.g., normal controls, early-onset

schizophrenia patients) and thus the findings from the characterization of the late-onset

psychotic disorder group as a whole was limited to descriptive purposes only. The series

also included only patients who presented to acute psychiatric service and therefore our

findings may represent the more severely ill patients with late-onset psychotic disorder,

and not reflect the full spectrum of cases in the population. Furthermore, although the

cases in this series were followed prospectively after their first presentation to the acute

psychiatric service, their DSM-IV-based diagnoses of schizophrenia and delusional

disorder were made via a retrospective chart review. This limitation is a consequence of

the real-world confusion and controversy that has plagued diagnostics in this population

over the years. During the retrospective diagnostic review, for example, it became clear

that in many cases, the initial treating psychiatrists struggled to diagnosis a new-onset case in an elderly individual as "schizophrenia", although criteria for schizophrenia was met. Fortunately, very detailed chart records were available that included clinical observations from a number of clinicians (e.g., psychiatrist, psychiatric nurse, social worker) to form the basis of the retrospective re-classification of patients. Nevertheless, ideal circumstances would have been to classify each patient based on a structured diagnostic interview at presentation and at future follow-ups. Despite the large number of validators that were tested in this study, there are several validators that were not collected. This includes structured assessments of temperament and personality correlates, and research grade neuroimaging evaluations.

Conclusion & Future directions

In the face of an aging demographic, we can expect to see a growing number of older patients with psychiatric illness (Jeste, 2000) including those with late-onset psychotic disorder. Unfortunately, on a whole there is a relatively limited amount of useful information for this group of patients despite being first described over a century ago. This is reflected by the fact that the first randomized clinical trial of antipsychotic treatment is only underway now. A major reason for this current predicament has been the ongoing confusion and controversy surrounding the concept and terminology of this clinical presentation despite recent efforts at clarification (Howard et al., 2000). Furthermore, there has been a notable lack of studies that are prospective in nature and of a sufficiently large sample size. Despite these issues, a rather consistent picture of late-

onset psychosis has emerged across studies, which seems to speak to the fact that it is a single group of patients.

In the current study, consistent with previous work, the prevalence of negative symptoms, significant thought disorder and catatonia were substantially lower than in early-onset schizophrenia. This leaves two relatively arbitrary criteria – bizarreness and prominence of hallucinations – as the only two diagnostic criteria for distinguishing delusional disorder from schizophrenia in the vast majority of late-onset patients. With bizarreness being removed from the next iteration of the DSM, we will have only prominence of hallucinations to distinguish between these diagnostic groups. As evidence mounts that in the late-onset population these diagnostic groups of schizophrenia and delusional disorder have the same demographics, clinical presentation and course, response to treatment and other factors, it becomes more and more reasonable to consider them as a single diagnostic entity. It is less clear that the small minority of patients who do have negative symptoms, formal thought disorder and/or catatonia can be considered part of the same group. While it is possible that this minority is indeed a similar group but further along the spectrum of severity, it is also possible that this group represents a different entity (e.g., in keeping with "classic" early-onset schizophrenia). This is certainly an area for future research.

In conclusion, our study supports a single diagnostic group for patients over the age of forty presenting with new-onset psychosis in the absence of a dementing or

affective illness or primary medical/neurological cause based on an assessment of antecedent, concurrent and predictive validators. We suggest the diagnosis of "Late-Onset Psychotic Disorder" for this group of patients. We selected this diagnostic term rather than to perpetuate the use of "schizophrenia" as recommended by Howard et al. (2000) for two main reasons – i) the inclusion of patients who had been previously diagnosed as delusional disorder, and ii) the mounting evidence to suggest that late-onset psychotic disorder is neurodegenerative in nature in contrast to the current conceptual understanding of schizophrenia as a neurodevelopmental illness – although this remains an issue of debate given the absence of known etiopathophysiological mechanisms. Although it has been recommended to distinguish middle-onset (e.g., 40-60 years old) from very-late-onset (e.g., over 60 years old) (Howard et al., 2000) there is a current lack of clinical evidence to support this division (e.g., Girard & Simard, 2008) and more research is required to determine if this is in fact a valid distinction.

More than ever, there is a need for a valid (and/or useful) diagnosis to ensure reliable and efficient identification of subjects for research progress in terms of the underlying cause(s), the clinical management and the course of illness for this patient group. For the former, focus should be on the interrelationship between normal ageing processes, medical/neurological comorbidities (e.g., vitamin B12 deficiency, cerebrovascular disease and its risk factors) and the onset of psychosis. Further study of the relationship between late-onset psychotic disorder and the development of dementia is warranted, and could potentially lead to the optimization of treatments and improved

understanding of the underlying disease processes. The development of collaborative specialty geriatric psychiatry clinics at academic centres serving late-onset psychotic disorder patients over the course of their illness would be ideal settings for such research to take place. As anticipation grows for the publication of the DSM-V in 2013, aimed at developing "more useful ways of classifying and diagnosing mental disorders" (Kendler et al., 2009), it is the opportune time to finally bring clarity to the "darkest area of psychiatry" (Bleuler, 1943).

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Appendix 1.

DMS-IV-TR (APA, 2000) Diagnostic criteria for Schizophrenia

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

(1) delusions

(2) hallucinations

(3) disorganized speech (e.g., frequent derailment or incoherence)

(4) grossly disorganized or catatonic behavior

(5) negative symptoms, i.e., affective flattening, alogia, or avolition

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective and Mood Disorder exclusion: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a Pervasive Developmental Disorder: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Appendix 2.

DSM-IV-TR (APA, 2000) Diagnostic criteria for Delusional Disorder

A. Nonbizarre delusions (i.e., involving situations that occur in real life, such as being followed, poisoned, infected, loved at a distance, or deceived by spouse or lover, or having a disease) of at least 1 month's duration.

B. Criterion A for Schizophrenia has never been met. Note: Tactile and olfactory hallucinations may be present in Delusional Disorder if they are related to the delusional theme.

C. Apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired and behavior is not obviously odd or bizarre.

D. If mood episodes have occurred concurrently with delusions, their total duration has been brief relative to the duration of the delusional periods.

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.