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Late-life psychosis in women and men

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Summary. Psychosis is a psychopathological condition characterized by a loss of contact with reality, pervasive thought and perception disorders and social and occupational function impairment. Although psychosis typically presents in the juvenile age, senile psychosis, i.e. with clinical presentations over the age of sixty-five, deserves special consideration, given its many different causes and diverse clinical expressions. It is estimated that the prevalence of psychotic disorders in the elderly population varies between 0.2% and 4.7% and reaches 10-63% amongst elderly patients who are hospitalized, especially in intensive care settings. It is more common in the female population and although the cause of this greater vulnerability is not known, it is thought that it may be associated with a higher concentration of dopamine receptors in the brain, as well as with the action of female sex hormones. Despite its high prevalence, senile psychosis remains a diagnostic and therapeutic dilemma. Firstly, a distinction must be made between very late-onset psychosis and that with an earlier onset that persists into old age. Secondly, a thorough differential diagnosis is essential: senile psychosis is defined as primary if the cause is a mental disorder and secondary if it is caused by a medical condition. In 60% of cases, very senile psychosis is secondary to neurological disorders, metabolic and endocrine disorders, infections, autoimmune diseases, or drugs/medicinal products. Psychosis can present in many different ways in the elderly and as the different disorders respond to different treatments, a scrupulous clinical analysis is of paramount importance.

Key words. Senile psychosis, elderly population, female population.

Psicosi in età avanzata nelle donne e negli uomini

Riassunto. La psicosi è una condizione psicopatologica caratterizzata da perdita del contatto con la realtà, disturbi pervasivi del pensiero e della percezione e compromissione del funzionamento sociale e lavorativo. Tipicamente presenta esordio in età giovanile; tuttavia la psicosi in età matura, ovvero con manifestazioni cliniche dopo i sessantacinque anni, merita speciale attenzione, in considerazione delle numerose cause e delle differenti espressioni cliniche. Si stima che la prevalenza dei disturbi psicotici nella popolazione anziana vari dallo 0,2% al 4,7% e raggiunga il 10-63% nei pazienti anziani ricoverati in casa di cura. Più di frequente interessa la popolazione femminile e la causa di tale maggiore vulnerabilità non è nota, per quanto si pensi sia correlata a una più alta concentrazione di recettori dopaminergici encefalici, oltre che all'azione degli ormoni sessuali femminili. Nonostante l'elevata prevalenza, la psicosi in età matura rimane un dilemma diagnostico e terapeutico. A tal proposito, bisogna distinguere la psicosi con esordio in età avanzata dalla psicosi ad esordio precedente che persiste in tarda età. In secondo luogo è essenziale un'accurata diagnosi differenziale: la psicosi in età matura può essere definita primaria se la causa è un disturbo psichiatrico o secondaria se la causa è una patologia medica. Nel 60% dei casi la psicosi in età matura è secondaria a disturbi neurologici, disordini metabolici ed endocrini, infezioni, patologie autoimmuni, droghe/farmaci. In conclusione, la psicosi può manifestarsi in modi differenti nell'anziano, e poiché i diversi disturbi rispondono a trattamenti distinti, è di fondamentale importanza un'accurata analisi clinica.

Parole chiave. Psicosi senile, popolazione anziana, popolazione femminile.

Introduction

Psychosis is a psychopathological condition characterized by a loss of contact with reality, pervasive thought and perception disorders and social and occupational functional impairment. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) does not provide a generic definition of psychosis. Consequently, when describing psychotic disorders, clinicians refer to the presence of Criterion A for schizophrenic psychoses, i.e. the existence of a clinical condition characterized by delusions, hallucinations, disorganized thoughts, disorganized (or catatonic) behavior and negative symptoms[1]. Psychotic disorders typically present in adolescence or early adulthood. However, it has been known for some time that psychoses can present at any age and that a significant percentage of people experience their first psychotic episode in old age[2-4]. Senile psychosis, i.e. with clinical presentations over the age of sixty-five, deserves special consideration, given its many different causes and diverse clinical expressions. Psychotic disorders in old age can be associated with early-onset schizophrenia that persists into old age, late-

onset schizophrenia (after 45 years of age), a schizoaffective disorder, delusional disorder or a mood disorder with psychotic characteristics. They can also present in association with autoimmune diseases, metabolic disorders, infections, delirium, cerebrovascular disease, brain tumors and a number of neurodegenerative diseases (in particular, Alzheimer's disease, Lewy body dementia, vascular dementia and Parkinson's disease). Lastly, senile psychosis can be caused by the use of psychotropic medicinal products and/or psychoactive substances[5]. Consequently, a distinction must be made between very late-onset psychosis and psychosis with an earlier onset that persists into old age. Secondly, it is essential to make a distinction between primary psychosis, i.e. that caused by a mental disorder, and secondary psychosis, i.e. that caused by a medical or neurological condition[6]. Although identifying the etiology of senile psychosis is difficult, the diagnostic work-up can be facilitated by the clinical presentations specific to each disorder. A thorough, early and prompt differential diagnosis is essential, as a great many serious medical conditions can be concealed by psychotic symptoms.

Epidemiology

Psychotic disorders are relatively common in old age. They have an estimated prevalence in the elderly population of between 0.2% and 4.7%, which reaches 10-63% amongst hospitalized elderly patients[7]. The lifetime risk of psychotic symptoms in the elderly population is 23%[6]. Senile psychosis is more common in the female population. The incidence of mental disorders is known to differ for males and females: it is estimated that in women the lifetime risk of developing a mental disorder is 37.6%, compared to 32% in men[8]. As far as psychotic disorders are concerned, during childhood and adolescence the incidence is similar for females and males. However, between 20 and 50 years of age, psychoses have a higher incidence in the male population, whereas over the age of 50, incidence rates are higher amongst women, and this difference becomes more prominent over the age of 80 (Figure 1)[4,8]. Although the cause of this greater vulnerability amongst elderly women is not known, it is thought to be associated with the different brain volume, the higher concentration of dopamine receptors and the action of female sex hormones[7]. In 60% of cases, very late-onset psychoses are secondary psychoses and are most commonly caused by neurodegenerative diseases[6,9,10]. The estimate prevalence of the conditions most commonly associated with psychotic symptoms in old age are listed in Table 1.

Table 1. Etiology of senile psychoses

	Evolution	Percentage	Type of psychosis
Mood disorders	Weeks-months	20	Primary
Schizophrenia spectrum disorders	Months-years	4	Primary
Dementia	Months-years	40	Secondary
Delirium	Days-weeks	12	Secondary
Psychoactive substances and alcohol	Days-months	11	Secondary
General medical conditions	Days-months	10	Secondary

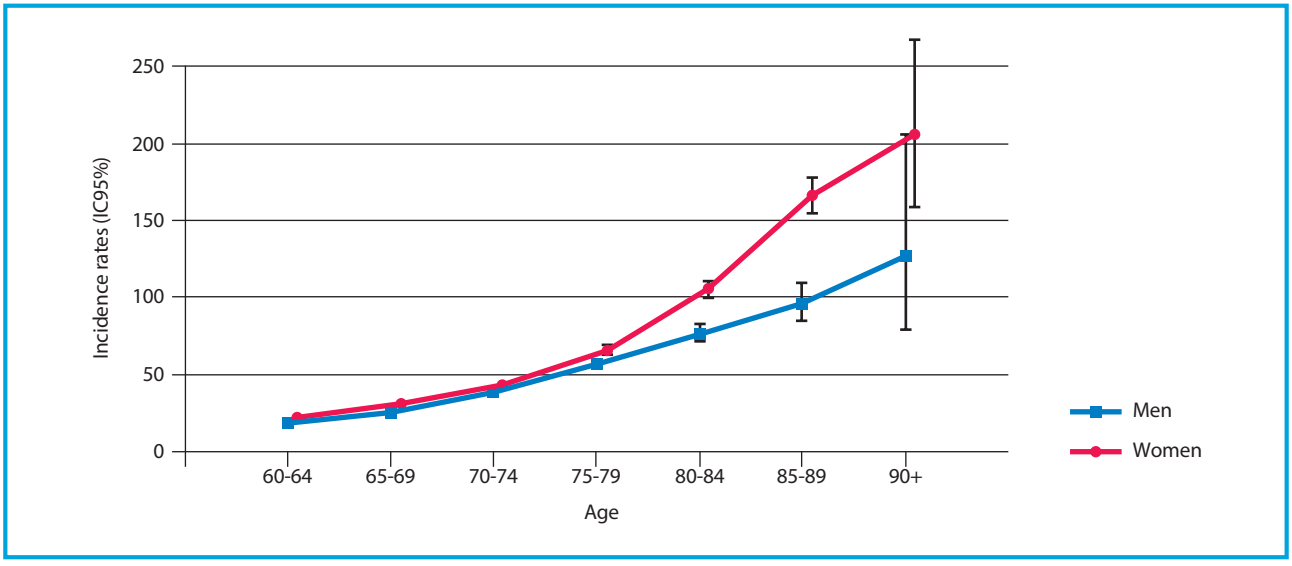

Figure 1. Psychotic disorder incidence rates per 100,000 people, by age and sex. Modified from Stafford et al, 2018.

Risk factors

Senile psychotic disorders require a thorough differential diagnosis as many serious medical conditions can be concealed by psychotic symptoms[11-13]. Identifying the risk factors for very late-onset psychoses is of fundamental importance to identifying the underlying condition. There are a number of risk factors associated with senile psychoses, including: social isolation, low social and academic status, stressful life events, sensory deficits, neurocognitive deterioration, medical comorbidities, concomitant mental disorders and polydrug use[14,15]. As there are no pathognomic signs allowing an easy distinction between the primary and secondary forms, all the potential causes of secondary psychosis must be ruled out before diagnosing primary psychosis.

In the differential diagnosis between the primary and secondary forms, it can be useful to differentiate the disorders according to the type of onset and the duration of the clinical symptoms, as shown in Table 1[6].

Clinical presentations

Secondary psychoses

In the DSM-5, mental disorders secondary to a general medical condition are defined as "disorders due to another medical condition". According to the DSM-5, a psychotic disorder due to another medical condition can be diagnosed in the presence of delusions and hallucinations that can be attributed to the physiological effects of a medical condition rather than of a mental disorder. A number of different considerations must be made to establish whether a psychotic disorder can be attributed to another medical condition.

A first consideration is the presence of a temporal association between the onset, exacerbation or remission of the medical condition and that of the psychotic disorder. A second consideration is the presence of characteristics that are atypical for a psychotic disorder (for example, late age of onset, presence of visual or olfactory hallucinations or severe disorientation to time and place). Further clinical presentations that can help to distinguish secondary psychoses from primary psychoses are: negative psychiatric history, no family history of mental disorders, partial response to psychotropic therapy, abuse of medicinal products or psychoactive substances, presence of medical comorbidities and presence of memory disorders[1]. Psychotic disorders in old age can present in association with a number of medical conditions, the most common being brain injuries, epileptic disorders, autoimmune conditions, cerebrovascular disease, brain tumors, infections, neurodegenerative conditions, endocrine and metabolic conditions and use of drugs and psychoactive substances. The disorders that most commonly cause secondary senile psychosis are shown in Table 2[6]. Amongst elderly subjects, psychotic disorders caused by a medical condition are more prevalent in females, although other gender-related aspects are not evident and vary considerably with the gender distribution of the underlying medical conditions. As regards the clinical presentations, although in secondary psychoses, hallucinations can affect any of the senses, certain etiological factors tend to cause specific hallucinatory phenomena. For instance, olfactory hallucinations are suggestive of temporal lobe epilepsy. Hallucinations can be simple and unstructured or highly complex and organized, depending on the etiological and environmental factors. Delusions can have a variety of

Table 2. Causes of secondary psychosis

Metabolic disorders	Electrolyte abnormalities
	Acute porphyria
	Hepatic encephalopathy
	Uremic encephalopathy
	Nutritional deficiencies (vitamin D, folates, etc.)
	Anoxia/hypoxia
	Hypercapnia
Infections	Meningitis
	Encephalitis
	Neurosyphilis
	HIV/AIDS
	Pneumonia
Neurological disorders	Brain tumours
	Epilepsy
	Subdural haematomas
	Cerebrovascular events
	Huntington's disease
	Multiple sclerosis
	ALS
	Parkinson's disease
	Alzheimer dementia
Autoimmune diseases	SLE
	Vasculitis
Endocrine and metabolic disorders	Hypo/hyperthyroidism
	Hypo/hyperglycemia
	Hypo/hyperparathyroidism
	Adrenal gland disorders

themes, but are most commonly of the persecutory type. As regards evolution, secondary senile psychotic disorders can have a transient isolated or recurrent nature or can be cyclical and follow the exacerbations and regressions of the underlying medical condition[16]. The identification and treatment of the underlying medical condition has the greatest impact on the evolution of the psychotic disorder, although in some cases the psychotic symptoms can persist for a long time after the medical event (for example, psychotic disorder secondary to focal brain damage). Lastly, when associated with chronic medical conditions, the psychosis can have a long-term evolution. It is of fundamental importance to identify the cause of the psychotic disorder, as the treatment of secondary psychosis is based on the treatment of the underlying medical disorder[16].

Delirium

According to the DSM-5, delirium is an attention or consciousness disturbance associated with a change in cognitive capacities. The attention disturbance presents with a reduced ability to focus, sustain or shift attention. The consciousness disturbance presents with an impaired orientation to the environment and place or, at times, even towards the self[1]. Delirium develops over a short period of time, usually between a hour and a few days, and the symptoms tend to fluctuate during the day. Delirium is also associated with cognitive changes (for example, memory loss, speech abnormalities, and changes in visuospatial abilities)[1]. Sleep-wake rhythm abnormalities and emotive disorders such as anxiety, fear and irritability are also common[17]. A diagnosis of delirium requires evidence, based on the medical history, physical exam or lab test results, that the phenomenon is the consequence of another medical condition, substance intoxication/withdrawal, exposure to a toxin or, alternatively, multiple etiologies that cannot be explained by another neurocognitive disorder[1]. The prevalence of delirium is higher amongst elderly subjects, especially when hospitalized. Indeed, it is estimated that the prevalence of delirium in the general population is low (1-2%) but increases with age, reaching levels of up to 14% amongst individuals over 85 years of age[1]. Risk factors associated with delirium are existing dementia, functional deficits, sensory deficits and history of alcohol or psychoactive substance abuse[17]. Sensory perception and thought changes are common in delirium: 12% of cases of senile psychosis are caused by delirium[18]. It is estimated that, depending on the population analyzed, between 40% and 70% of elderly subjects with delirium experience hallucinations and between 25% and 79% experience delusions[19-21]. Psychotic symptoms present more commonly as hyperkinetic delirium than hypokinetic delirium[19]. As regards evolution, in hospital settings, delirium usually lasts about a week, although some symptoms may persist for longer. Delirium can progress to stupor, coma, epileptic seizures or death, especially if the underlying cause is not treated. Early identification and swift intervention can reduce duration and improve prognosis.

Alzheimer's disease and other neurocognitive disorders

Neurocognitive disorders are characterized by attention, executive function, learning and memory, speech, motor perception and social cognition deficits[1]. There are a great many neurocognitive disorders, of which Alzheimer's disease is one of the most common: it is estimated that 7% of subjects over 65 years of age has Alzheimer's disease, which is more common in females[22]. Psychotic symptoms are extremely frequent in Alzheimer's disease, with an estimated prevalence of between 30% and 50%[23]. Generally speaking, psychotic symptoms are more common in hospitalized patients and the severity of the cognitive disorder correlates positively with the presence and severity of the psychotic symptoms[24,25]. In Alzheimer's disease, hallucinations are usually visual and delusions are usually simple, non-bizarre and have a persecutory nature. Parkinson's disease also often causes psychotic symptoms in the elderly population; in most cases, they present with visual hallucinations and more rarely with delusions, which are usually persecutory and non-bizarre, when present[26]. Unlike Alzheimer's disease, Parkinson's disease is more common in male subjects and the severity of the psychotic symptoms does not appear to correlate with the severity of the neurological disorder[27,28]. Lastly, psychotic symptoms are common in subjects with vascular dementia and Lewy body dementia. For diagnostic purposes, it is important to remember that in the elderly population psychotic symptoms secondary to dementia occur after the onset of the neurocognitive disorder[24,25].

Drugs, medicinal products and toxins

The essential characteristic of substance-induced psychotic disorder is the presence of hallucinations and delusions caused by the physiological effects of a substance. Consequently, there must be medical history, physical exam or laboratory test evidence of substance use, intoxication or withdrawal. Substance- or medicinal product-induced psychotic disorders occur during or shortly after exposure to the substance/medicinal product or following intoxication or withdrawal and they may last for some weeks[1]. Once they have appeared, the psychotic symptoms can persist for as long as use of the substance/medicinal product continues. Psychotic disorders can occur during intoxication from alcohol, cannabis, hallucinogens, inhalants, sedatives, hypnotics, anxiolytics and stimulants (including cocaine and amphetamines). Psychotic symptoms can also be observed during withdrawal from alcohol, sedatives, hypnotics

and anxiolytics. A great number of medicinal products can be associated with the onset of psychotic symptoms, including anesthetics, analgesics, anticholinergic agents, antiepileptic drugs, antihypertensives, anti-Parkinson drugs, corticosteroids, interferon and nonsteroidal anti-inflammatory drugs. Lastly, the toxins that can cause psychotic symptoms include, for example, insecticides, carbon dioxide, carbon monoxide and volatile substances such as petrol and paints. In the elderly population, psychosis caused by substance abuse is less frequent, whereas psychosis secondary to polydrug use is far more common[29].

Primary psychoses

Psychotic disorders are defined as primary when the cause is a mental disorder. In order to diagnose primary psychosis, all the potential causes of secondary psychosis must be ruled out, making it a diagnosis of exclusion[9,11]. In the elderly, primary psychoses can be associated with mood disorders and schizophrenia spectrum disorders.

Mood disorders

The second most common cause of senile psychosis, with a prevalence of 20% of diagnoses, are mood disorders[18]. Psychotic symptoms can be observed in subjects with major depressive disorder and bipolar disorder.

Major depressive disorder is a relatively common disorder in the geriatric population, with an estimated prevalence of approximately 3% in the general population and of 12-25% in institutionalized subjects[30]. Prevalence rates are 1.5 to 3 times higher in females than in males[1]. Although in the absence of concomitant conditions, depressive symptoms in the elderly maintain characteristics that are more or less identical to those of the other age groups, it is important to remember that there are certain symptoms that are more characteristic of senile depression. More specifically, somatic and cognitive symptoms prevail, with attention, concentration and memory deficits[31]. Most of the major depressive episodes diagnosed in the elderly are recurrences of mood disorders that presented earlier in life. In these cases, the symptoms tend to be more typical and the evolution is less often chronic. Major depressive disorder can present in old age (>65 years) and in this case has certain characteristic symptoms: these depressions have a longer duration, they are characterized by the prevalence of mixed, anxious and somatic symptoms and life events take on a greater importance as trigger events than hereditary constitutional predisposition. These kinds of depression tend to be very severe with a major suicide risk[32]. Psychotic symptoms are also common. Indeed, it is estimated that 40% of elderly patients hospitalized for depression presents thought disorders. Delusions are the most common psychotic symptoms and are usually mood-congruent, such as delusions of guilt, delusions of poverty, hypochondriacal delusions and negativism delusions. Sensory perception disorders are rarer and, when present, usually take the form of auditory misperceptions[33].

In most cases, the bipolar disorder presents at a young age. Type 1 bipolar disorder usually has an earlier onset between late adolescence and adulthood, between 15 and 40 years of age (on average around the age of 30), whereas type 2 bipolar disorder presents slightly later, at between 25 and 50 years of age. Whereas type 1 bipolar disorder has an equal distribution between the sexes, type 2 has a slightly higher frequency amongst females. It is estimated that 90% of patients with bipolar disorder has a first affective episode before the age of 50. Consequently, in 10% of cases the disorder presents after the age of 50. The prevalence of bipolar disorder in the elderly population is 0.1% and in selected populations, such as institutionalized patients, it reaches 10%[34]. The etiopathogenesis of senile bipolar disorder is complex. Indeed, the disorder can be broken down into two subtypes: the first, bipolar disorder with an earlier onset that persists into old age, the second, bipolar disorder with a late onset. Whereas there is very strong familiarity for the first subtype, late-onset bipolar disorder presents a less significant hereditary constitutional predisposition. Very late-onset bipolar disorder has a number of specific clinical characteristics: primarily depressive polarity, more frequent and more moderate manic episodes, frequent mixed symptoms, multiple medical and neurological comorbidities[34-37]. Psychotic symptoms are common during major depressive episodes and mood-congruent and somatic delusions usually prevail. It has also been demonstrated that in elderly patients with a late onset of manic episodes the risk of developing stroke or other cerebrovascular disorders is twice as high. The most accredited etiopathogenetic hypotheses include the vascular hypothesis that correlates cerebrovascular damage with the onset of manic episodes in old age[38].

Schizophrenia spectrum disorders

Schizophrenia typically has a juvenile onset with an equal distribution between the sexes. There are usually two gender-correlated incidence peaks: the earlier peak occurs in males (14-24 years), and the later peak in females (25-35 years). Nevertheless, in 23.5% of cases, schizophrenia has a late onset after the age of 45 and typically presents in females[39]. It has also been observed that in 0.3% of cases schizophrenia presents after 65 years of age[40]. Schizophrenia can therefore either have an early onset and persist into old age or present for the first time in old age. Subjects with late-onset schizophrenia more often experience visual, tactile or olfac-

tory hallucinations or derisive auditory hallucinations. Persecutory and bizarre delusions are also common. Formal thought disorders and negative symptoms, on the other hand, are usually moderate and rare[41-46]. However, a reduction in positive symptoms is observed in elderly subjects with early-onset schizophrenia persisting into old age. In a smaller percentage of cases, senile psychosis presents in association with schizoaffective disorder or delusional disorder. Schizoaffective disorder, like schizophrenia, typically has a juvenile onset, although cases with a senile onset have also been described. There are two subtypes of schizoaffective disorder: the bipolar type and the depressive type. Whereas the bipolar type usually presents in young adults, the depressive variant is more common in old age[47,48]. Although delusional disorder usually presents in the adult age, certain cases with a senile onset have also been described. The delusions can have a variety of themes; they are most commonly of the persecutory type and reported to regard the family environment, they are unsystematized and favored by concomitant sensory deficits.

Treatment

The treatment of senile psychosis varies according to the context in which the psychotic disorder presents. Consequently, the treatment of secondary psychoses focuses on the identification and treatment of the underlying medical condition. Conversely, depending on their etiology, primary psychoses require the administration of mood stabilizers, antidepressants and antipsychotics. The use of psychotropic drugs in the elderly requires special attention, given the age-related difficulties in terms of pharmacokinetic abnormalities, medical comorbidities and polydrug use. Although the use of mood stabilizers in the elderly has been seen to have a similar efficacy to that observed in other age groups, they should be administered with caution in the elderly, given the pharmacokinetic and pharmacodynamic changes and the different tolerability. Antidepressant use in elderly subjects requires special attention considering the risks of cardiovascular, hematological and osteoarticular disorders[49,50]. As regards antipsychotics, their use in elderly subjects can be difficult, due to their many and often very severe side effects. The most common adverse events in the geriatric population are extrapyramidal symptoms: the elderly are sensitive to the onset of muscle stiffness, bradykinesia, tremors, akathisia and dystonia. Extrapyramidal symptoms are most often associated with the use of typical antipsychotics. Another severe side effect is tardive dyskinesia, a serious disorder characterized by involuntary movements, usually involving the orofacial region. The annual incidence of tardive dyskinesia in juveniles on antipsychotic treatment is 4-5%, but rises to 30% in subjects over the age of 45. Indeed, adults, especially the elderly, have a 4-5 times greater risk of tardive dyskinesia than the juvenile population[51]. A number of studies have shown that the tardive dyskinesia incidence rates are statistically lower in patients treated with atypical antipsychotics than those treated with typical antipsychotics[7,52,53]. Consequently, the use of typical antipsychotics in the elderly population requires special attention and monitoring by the clinician and, when possible, atypical antipsychotics should be preferred. Nevertheless, weight gain, dysmetabolic syndrome and metabolic syndrome can be severe complications of therapy with second-generation antipsychotics. Not all atypical antipsychotics present the same risk of metabolic side effects. Paliperidone palmitate has shown efficacy in the treatment of severe psychotic disorders and has a safer metabolic profile than other medicinal products in the same class[54]. Lastly, the most severe side effect associated with the use of antipsychotics in elderly patients is the increased risk of death. It should be remembered that in 2005, the FDA issued a black box warning regarding the prescription of atypical psychotics in elderly subjects with psychosis secondary to dementia, due to an increased risk of mortality (mainly due to cardiovascular events and infection) compared to placebo. In short, the use of typical antipsychotics in elderly subjects requires a careful and thorough assessment by the clinician, as well as close monitoring.

Conclusions

Senile psychosis deserves special consideration, given its many different causes and diverse clinical expressions. A timely and accurate differential diagnosis is essential, as a great many serious medical conditions can be con-

Key messages
■ Senile psychosis is a common clinical condition.
■ It may present either during old age or at an earlier time and persist into old age.
■ It can be primary, i.e. caused by a mental disorder, or, more commonly, secondary, when it is caused by a medical or neurological disorder.
■ A thorough differential diagnosis is essential as the different psychotic disorders respond to different treatments.
■ The use of psychotropic drugs in the elderly warrants thorough a careful evaluation by the clinician.

cealed by psychotic symptoms. Indeed, in the elderly, psychosis is often secondary to medical or neurological conditions and is only primary, i.e. determined by mental disorders, in a lower percentage of cases. As the different disorders respond to different treatments, a scrupulous clinical analysis is of paramount importance. The choice of treatments requires careful and thorough consideration by the clinician, given the many common side effects with which psychotropic drugs can be associated, especially in this patient population.

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