Psychosis in the Elderly

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Abstract

Psychosis in the elderly represents a frequent and challenging feature, with a prevalence of psychotic symptoms that may reach 10–63% in the hospitalized population. However, both the diagnosis and the treatment of psychotic symptoms in the elder population may present many problems.

In the present chapter, we debate the differential diagnosis between the causes of psychosis in the elderly and how to deal with them. The first cause of psychosis in this population is represented by dementia. Psychiatric symptoms may be present not only in the last phases of neurodegenerative disorders but also in the early stages or at onset, more frequently in specific subtypes of dementia, such as frontotemporal dementia. The second most common cause of psychosis in the geriatric population is depression, while delirium is the third. Delirium, differently from the other described diagnoses, is characterized by an acute change in mental status, disturbances of consciousness, and clouded sensorium and may be caused by several circumstances, ranging from infections to inappropriate medication use.

Considering the background of the present literature, we report the case of a 66-year-old man who was referred to our inpatient clinic for a manic episode with delusions. We investigated the differential diagnostic processes, which encompass a comprehensive clinical evaluation, a very accurate anamnestic interview, blood tests, and eventually brain imaging. Another major issue of concern is treatment, which might be guided by a multidisciplinary endeavor, including pharmacological and non-pharmacological interventions.

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3.1 Introduction

Psychosis in the elderly represents nowadays one of the major challenges to clinicians. The elderly are expected to reach 20% of the general population by the year 2030 [1], with an increased concern about problematics in this specific population. Prevalence of psychotic disorders in the elderly ranges widely from 0.2 to 4.75% in community-based samples but may reach 10–63% in the hospitalized population. As the population ages, the interest in psychotic symptoms in aged people is also increasing; however recognition of psychosis is complex due to patients that often deny this kind of symptomatology as a psychological dimension, presenting somatic complaints, anxiety, or cognitive impairments [2].

However, diagnosis and treatment of psychotic symptoms in the elderly population may present many problems, as we will review in this chapter, exemplifying the difficulties clinicians confront with in dealing with such a complex population. Psychosis, indeed, not only represents an acute problem to face but also accounts for poor prognosis, suffering, and social withdrawal [3].

3.1.1 Differential Diagnosis

The diagnosis of psychosis in the aged population needs the collaboration of an interdisciplinary team, with a full clinical, psychiatric, and neurological assessment. The differential diagnosis of elderly patients that present with delusions, hallucinations, and behavioral disturbance should include psychosis related to delirium, psychosis due to general medical conditions, atypical dementia onset, behavioral and psychological symptoms of dementia (BPSD), affective illness, schizophrenia, bipolar disorder (BD) or other primary psychotic disorders, and substance abuse or dependence [4]. Moreover, interactions between different clinical conditions are possible: patients with dementia may have a lower threshold for delirium, and similarly mood alterations may be a prodrome for dementia [5].

Overall, dementia is the most common cause of psychosis in the geriatric population, accounting for almost 40% of the cases [6]. Psychosis is a major aspect of neurodegenerative processes and poses an important health concern for the aged population. Psychiatric symptoms may be present not only in the last phases of neurodegenerative disorders but also in the early stages or at onset [7]. Psychotic symptoms, indeed, are often present in both Alzheimer's disease (AD) and in the behavioral variant of frontotemporal dementia (bvFTD) [8]. As widely reported in the literature, psychosis is one of the most frequent non-cognitive symptoms of AD, with prevalence ranging from 30 to 50% [6]. Moreover, thought disorders seem to be

associated with poorer prognosis and greater cognitive impairment [7]. Regarding bvFTD, a large majority of the subjects suffered from delusions, hallucinatory behavior, or suspiciousness during the course of their illness. bvFTD is often associated with heterogeneous presentations, including pure psychiatric symptoms [9], and hallucinations and delusions can even precede the onset of cognitive symptoms and are often recognized as the clinical onset of the disease [10]. From previous studies, a correlation between psychotic symptoms in bvFTD and C9ORF72 hexanucleotide repeat expansion clearly emerges, indicating a possible genetic vulnerability to psychosis in this specific population [7, 11]. Regarding the clinical presentation, delusions of patients affected by dementia are often simple, usually of a paranoid nature, where patients believe that items have been stolen from them or that they have been abandoned [6].

According to literature, the second most common cause of psychosis in the geriatric population is depression, accounting for more than 20% of diagnoses [2]. Subjects with previous diagnoses of mood disorders are at risk of recurrence. On the other hand, late-onset depression (age $>$ 65 years) is also possible, even though it seems to be a different subtype of depression. The prevalence of major depressive disorder (MDD) in the elderly is estimated at 1–3%, although recognition of depressive symptomatology is complex due to patients that often deny depression as a psychological dimension, also presenting somatic complaints, anxiety, or cognitive impairments [12, 13]. It usually shows a peculiar presentation in terms of symptomatology: late age onset depression is more likely to be psychotic and often characterized by delusion focused on somatic concern (hypochondriacal), persecution, guilt, and nihilistic content more frequently than early-onset depression [14]. Moreover, previous literature indicates that late-onset depression is associated with higher prevalence of psychosis [15] and might be a prodrome of further developing dementia, especially AD [16].

Delirium is the third most common cause of psychosis in the elderly [17]. Delirium, differently from the other described diagnoses, is characterized by an acute change in mental status, disturbances of consciousness, and clouded sensorium that might be accompanied by abnormalities in mood, perception, and behavior. Delirium is commonly classified into hyperactive delirium, hypoactive, mixed, and the non-motor subtype. Although hypoactive delirium is usually the most common subtype among hospitalized geriatric patients, psychotic features seem to be more associated with hyperactive delirium subtypes [18]. The geriatric population is particularly at risk of developing delirium, which is described as affecting up to 50% of the elderly hospitalized population, showing a medical and/or multifactorial etiology [19]. A pre-existing medical condition could predispose to delirium or to a psychotic disorder due to a general medical condition. Uncontrolled diabetes, pulmonary or urinary tract infections, and electrolyte alterations are the most common causes of delirium in the elderly. Also misuse or abuse of prescription drugs (such as benzodiazepines) may lead to delirium. Inappropriate medication use in the elderly is the cause of many hospital admissions and may trigger psychotic symptoms (for a more comprehensive review of inappropriate medication use in the elderly, we suggest the Revised Beers Criteria, [20]). Moreover, there might be

an intertwining interaction between dementia and delirium, with delirium as a marker of vulnerability to dementia [21].

Other causes of psychotic symptoms in the elderly encompass previously diagnosed psychotic disease, such as schizophrenia, paranoia, and bipolar disorder, and worsening or onset of clinical and neurological conditions, such as brain neoplasia.

Box 3.1 Differential Diagnosis of Psychosis in the Elderly

- *Dementia*: both AD and bvFTD; also in the early stages or at onset
- *Depression*: often with somatic concern (hypochondriacal), persecution, guilt, and nihilistic content
- *Delirium*: acute change in mental status, often due to medical conditions of drug misuse
- *Neurological condition: i.e., brain tumor, brain abscess, etc.*
- Previously diagnosed psychotic disease: i.e., schizophrenia, paranoia, bipolar disorder, etc.

3.1.2 Clinical Evaluation

A comprehensive clinical evaluation is necessary to determine what may be the causes of the psychotic symptoms and to rule out possible etiologies. A wide range workout including psychiatric, neurologic, and medical assessment, as well as blood, urine, brain, cardiac, and imaging studies should be carried out.

A very accurate anamnestic interview should be performed at the admission, with the help of relatives or caregivers. The interview should include previous psychiatric or neurological history, ongoing medical conditions, and pharmacological history.

Clinical acuity of the presentation and intervention impact should guide the evaluation, according to the history and initial examination. Of the three most common psychosis-causing diseases (delirium, depression, and dementia), delirium is usually the most acute and caused by acute and potentially reversible medical conditions. Within a context of frailty and limited reserve capacities, several stressors and intertwining pathological mechanisms may lead to imbalance in the normal homeostasis. Several conditions, therefore, must be assessed. Blood and urine exams, along with vital signs, should be performed as soon as possible, to determine whether an infection has occurred. In elderly patients, urinary tract and pulmonary infections are usually the most common [22], both in hospitalized and in outpatients. Uncontrolled diabetes mellitus and hydro-electrolyte alterations are also common causes of acute delirium and should be assessed as soon as possible, given the fact that all the conditions are reversible with appropriate treatment. Constipation as well as acute and chronic pain represents other reversible causes of delirium that can be promptly treated.

Plasma levels of daily medications prescribed to the patients should be assessed, for measurable drugs. Many psychiatric and nonpsychiatric treatments may be the cause of agitation, confusion, and delirium, if the dosage is above a certain threshold.

A computed tomography (CT) scan should be performed in the case of altered/clouded sensorium and other neurological symptoms of acute onset, to exclude neurological/neurosurgical conditions, such as stroke and intracranial hemorrhage. After the exclusion of the most acute and dangerous causes, a full psychiatric assessment should be performed. Overall, it is of fundamental importance to conduct a full brain imaging assessment, consisting of magnetic resonance imaging (MRI) and positron emission tomography (PET), that may greatly help in the diagnostic processes of dementia [23].

Another major issue of concern is treatment, which might be guided by a multidisciplinary endeavor, including pharmacological and non-pharmacological interventions. The choice and dosage of pharmacological medications should be guided not only by efficacy but also by potential side effects and unwanted interactions with other medications. Drugs' starting doses are usually lower compared to those recommended for younger adults and should be titrated up or down slowly according to clinical response and side effects onset. Overall, treating elderly patients presents more difficulty because of greater sensitivity to drugs and their side effects, higher rates of polypharmacy, and variation in the pharmacokinetic parameters [24]. The drug plasma levels do not correlate with clinical improvement in the elderly population, and this could be explained by an increase in side effects that may aggravate the discomfort felt by the patient [25].

Box 3.2 Exams and Assessment

- Accurate interview with the patient and caregivers
- Physical examination with vital signs
- Blood and urine exams, looking for infections, alteration in electrolytes, uncontrolled metabolic conditions (diabetes)
- Plasma levels of prescribed medications and drugs of abuse
- Brain imaging: CT scan in acute; MRI and PET to assess neurodegenerative disorders (in selected cases)

3.2 Case Presentation

In January 2017, a 66-year-old man was referred to our inpatient clinic for a manic episode with delusions. No previous psychiatric history had been reported before the actual admission. He had no a family history for psychiatric disorder. Neither substance abuse nor medical comorbidity was reported by the patient. At the time of the admission, he was not taking any psychiatric medications except for 10 mg of zolpidem in order to sleep. Regarding other medications, the patients reported taking 10 mg of enalapril for a mild hypertension.

He reported a recent history of stressful events (working pressure) prior to the onset of symptoms. The patient graduated in law and had a good career as a lawyer. However, he had not been working in the last month before the admission.

At the time of evaluation in the emergency room, he showed dysphoric mood, psychomotor acceleration, severe insomnia, and aggressiveness; persecutory and jealousy delusions were also referred by the patient. He firmly refused hospitalization; however, a compulsory hospitalization was necessary.

During his stay in our inpatient unit, blood and urine exams were performed. No significant data emerged from the blood exams, except for a total cholesterol above the normal threshold (chol 235 mg/ml). The urine drug screening was negative for common drugs of abuse. He underwent the Brief Assessment of Cognition in Schizophrenia (BACS), which showed a deficit in the executive functions, frontal efficiency and motor proficiency, and poor performances, just barely above the deficit cutoff, in verbal fluency and working memory, as shown in Table 3.1.

We performed encephalic magnetic resonance imaging (MRI), electroencephalography (EEG), and fluorodeoxyglucose positron emission tomography (FDG-PET). The EEG resulted negative for anomalies, except for unspecific theta waves in the frontotemporal electrodes. The MRI resulted in a moderate atrophy in the parietal lobe and scattered white matter hyperintensities, probably of vascular origins, more prominent in the left hemisphere (Fig. 3.1). The PET did not evidence any significant modification in the normal and symmetric brain metabolism (Fig. 3.2).

A neurologic evaluation was performed and resulted negative for gross alterations. However, the neurologist suggested researching C9ORF72 hexanucleotide repeat expansion and progranulin mutation, which resulted negative as well.

As a pharmacological treatment, he was administered intramuscular aripiprazole 30 mg/d and daily oral valproic acid 1000 mg. The patient presented a good response in terms of reduction of delusions and psychomotor acceleration, as presented in Fig. 3.3. After a few days of treatment, he became more aware of his condition and accepted both the stay in the acute ward and the treatments. However, a full compliance to pharmacological treatment was not completely achieved as the patient

Table 3.1 Neurocognitive evaluation assessed by BACS subtest

Test	Normal score	Score	Comment
Language			
Verbal fluency	≥31.68	33.25	*Low score, just above threshold*
Memory			
Verbal memory	≥33.01	42.50	Normal
Motor proficiency			
Token task	≥68.77	57.50	**Deficit**
Symbol-coding task	≥40.49	30.50	**Deficit**
Frontal proficiency			
Working memory	≥14.93	15.50	*Low score, just above threshold*
Tower of London	≥12.37	10.50	**Deficit**
Frontal proficiency battery	>13.50	9.00	**Deficit**

Italic and Bold emphasis highlights the clinical importance for this kind of results

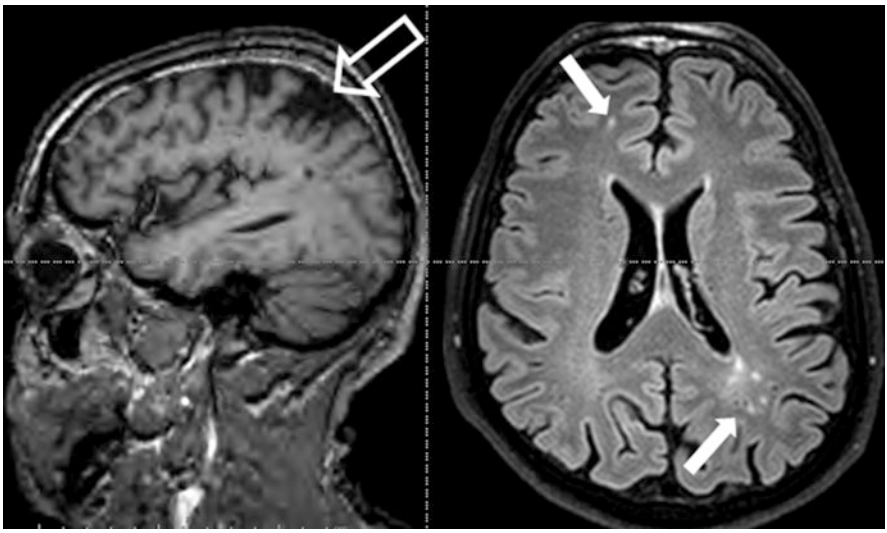

Fig. 3.1 Left panel: T1-weighted sagittal image showing moderate atrophy in the parietal lobe (empty arrow). Transverse Flair image showing white matter hyperintensities more prominent in the left posterior hemisphere, but visible also in the right frontal subcortical regions (full arrows)

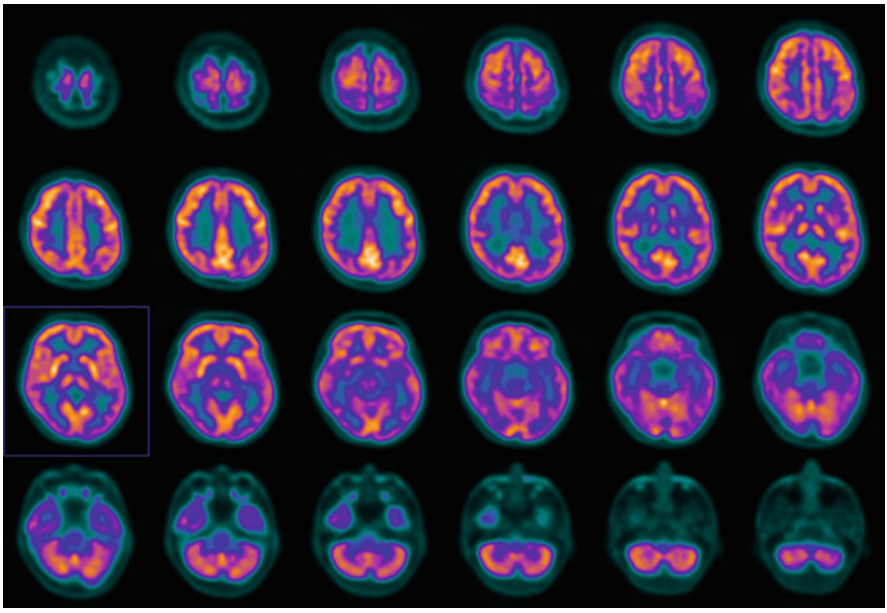

Fig. 3.2 FDG-PET shows no significant alterations of the normal symmetric glucose metabolism of the brain

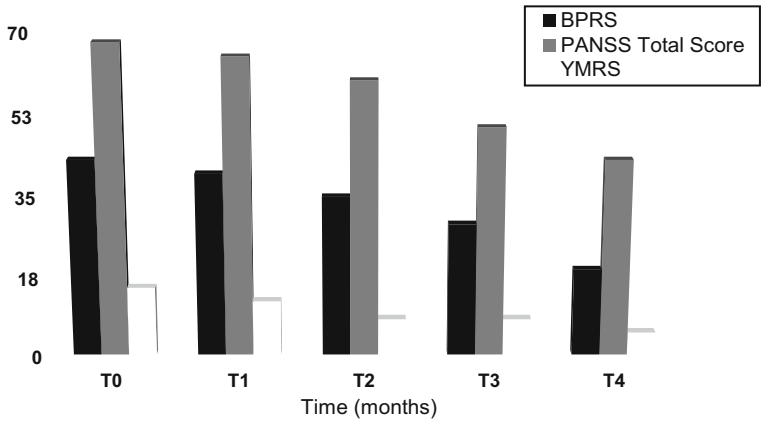

Fig. 3.3 Psychopathological rating scale (mean ± SD) time course

still didn't show full insight into his disease. From the clinical presentation and the response to treatment, a diagnosis of late-onset bipolar disorder type 1 was made. As a consequence of poor compliance, a program to dismiss the patient with a depot therapy was implemented. After discharge, he accepted monthly long-acting injection (LAI) with aripiprazole (400 mg). For the first month of treatment, it was administered an oral supplementation of aripiprazole 20 mg/d. The patient showed a response to treatment after 1 month and reached complete remission after 3 months. Aripiprazole plasma levels ranged from 48 ng/mL to 127 ng/mL. He has not presented any relapses to date (May 2017). The patient did not report any significant adverse effects, and changes in blood examinations did not appear during the follow-up period.

3.3 Literature Review

The presented case regards the difficult approach with late-onset bipolar disorder. Evidence suggest that bipolar disorder might have a trimodal distribution pattern of age of onset, namely, onset in late teens, mid-20s, and early 40s [26, 27]. Differences in clinical presentations between these groups appear nonsignificant. On the other hand, the late-onset subtype has often been recognized as a slightly different entity, overlapping sometimes with neurodegenerative disorders [28]. The onset of mania in later life might be indicative of an underlying medical comorbidity and should be assessed and investigated very carefully.

Neuroimaging studies showed several differences between late-onset bipolar disorder and early-onset bipolar disorder. Volumetric differences in specific frontal and temporal regions and white matter hyperintensities represent the most common

findings [29]. Moreover, neurodegenerative disorders share many features with late-onset bipolar disorder, making it difficult to disentangle. Behavioral and psychological symptoms in dementia might resemble the common disinhibition found in acute mania, and both conditions might present psychosis [30]. Apart from the clinical perspective, neurodegeneration and mood disorders seem to share many other aspects. The same inflammation and oxidative stress biomarkers have been identified for both Alzheimer's disease and mood disorders [31]. Moreover, late-onset bipolar disorder seems to share many genetic risk factors with frontotemporal dementia. Indeed, genetic mutation of progranulin and C9ORF72 hexanucleotide repeat expansion, commonly found in frontotemporal dementia, has been associated also with bipolar disorder [32–34], although a large sample study assessing the differences between the two diseases is still lacking.

Although in the presented case, genetic mutations were absent, we cannot rule out the possibility of a neurodegenerative disorder with a subtle psychiatric onset. In this hypothesis, neurocognitive assessment and brain imaging find its place. Our patient presented wide neurocognitive deficits, in several areas, namely, executive functions, working memory, and verbal fluency, which are in contrast with his high educational level and his current profession. The reported difficulties in dealing with working pressure before admission might be the consequence of an altered cognitive state. Moreover, the MRI showed a moderate atrophy in the parietal lobe along with multiple spots of probable vascular origin. The PET, on the other hand, seemed nonsignificant for any ongoing metabolic process alterations. These data, although non-specific for a neurodegenerative diagnosis, underlie a clear, general suffering of the brain. However, a direct relationship between the degree of brain damage and the clinical manifestations is often lacking [35]. Modern research considers the theoretical concept of "cognitive reserve" as a possible explanation for this discrepancy. It refers to structural and dynamic capacities of the brain to buffer against lesions and might be dependent on a naturally existing interindividual variability or modulated by lifestyle factors, such as physical activity, stimulating cognitive activity over a lifetime [36]. Major brain imaging anomalies are common findings in late-onset bipolar disorder [29]. A possible explanation might be that acute, acquired, possibly vascular events may impact on a genetic predisposition.

The choice of a treatment is another great issue in late-onset psychosis. The balance between effectiveness and adverse effects should be the guide. In this case, aripiprazole was the chosen molecule. Specifically, aripiprazole lauroxil (400 mg monthly) showed good effectiveness as mood stabilizer of a psychotic bipolar patient after a manic episode (Fig. 3.3). In addition, the patient did not develop adverse effects or presented metabolic changes. Aripiprazole is considered a safe and effective drug, with low rate of adverse effects [37]. Aripiprazole therefore may be a therapeutic option in cases similar to those presented in the present case (severe symptoms, psychotic features, and poor compliance to pharmacological treatment). In addition, the treatment with first-generation antipsychotics does not seem to significantly change the long-term outcome of psychotic bipolar patients [38]. Second generation antipsychotics have demonstrated stabilizing properties in bipolar disorder, but until now data about the use of atypical antipsychotic LAI are very

limited [39]. If future research confirm the efficacy of atypical antipsychotic LAI in the long-term treatment of BD (similarly to schizophrenia), these formulations may not be limited to the treatment of very severe patients, but they might be considered as early as possible in the course of BD. Finally, the stabilizing properties of atypical antipsychotics including aripiprazole would support the change of their obsolete name to "multidimensional stabilizers."

Plasma level determination is advisable during the long-term treatment to optimize the dosage and to investigate a possible correlation with clinical stabilization. These results, although not conclusive, may challenge the current therapeutic ranges proposed for antipsychotic drugs, most likely reflecting oral administration. Aripiprazole LAI showed its efficacy in the clinical stabilization of patients. The absence of severe adverse events demonstrated the tolerability of aripiprazole LAI. For this reason it should be considered an optimal maintenance treatment for bipolar disorder, regardless of the age of onset.

In conclusion, aripiprazole LAI showed its efficacy in the clinical stabilization of patients. The absence of severe adverse events demonstrated the tolerability of aripiprazole LAI, and for this reason it should be considered an optimal maintenance treatment for BP-I also in the elderly.

Key Points

- The elderly are at increased risk for psychosis because of age-related deterioration of cortical areas and neurochemical changes, comorbid physical illnesses, social isolation, sensory deficits, and polypharmacy. The prevalence of psychiatric and neuropsychiatric disorders requiring treatment with an antipsychotic agent is expected to increase dramatically among people aged >64 years.
- The differential diagnosis of elderly patients that present psychotic episode, for the first time, should include psychosis related to delirium, psychosis due to general medical conditions, atypical dementia onset, behavioral and psychological symptoms of dementia, affective illness, schizophrenia, bipolar disorder or other primary psychotic disorders, and substance abuse or dependence.
- Neuroimaging studies showed several differences between late-onset bipolar disorder and early-onset bipolar disorder. Volumetric differences in specific frontal and temporal regions and white matter hyperintensities represent the most common findings, so it is very important to assess the patient with neuroimaging procedures.
- Age-related changes in cognitive function vary considerably across individuals and across cognitive domains, with some cognitive functions appearing more susceptible than others to the effects of aging, and the mapping of cognitive processes onto neural structures constitutes a relatively recent research enterprise driven largely by advances in neuroimaging technology, so it is very important to assess the patient's cognition.
- Plasma level determination is advisable during long-term treatment to optimize the dosage and to investigate a possible correlation with clinical stabilization.

- For patients with psychosis who will not or cannot take oral medications on a regular daily basis or whose other characteristics, such as memory, vision, or auditory impairment, contribute to partial compliance, long-acting injectable antipsychotic medication offers a solution. Older patients are especially at risk of adverse effects associated with traditional antipsychotic agents, such as motor effects, postural hypotension, excessive sedation, and anticholinergic effects because of age-related pharmacokinetic and pharmacodynamic factors, coexisting medical illnesses, and concomitant medications. Therefore, drug dosage recommendations in the elderly are much more conservative than in younger patients.

Self-Assessment Questionnaire

1. What is the best therapeutic option for the stabilization of late-onset bipolar disorder?
   (A) Lithium
   (B) Valproic acid
   (C) Lamotrigine
   (D) Antipsychotic
2. What is the most frequent differential diagnosis that could be confusing in an elderly person presenting psychotic symptoms?
   (A) Dementia
   (B) Unipolar depression
   (C) Delirium
   (D) Brain neoplasia
3. What is the most frequent volumetric difference found between late-onset bipolar disorder and early-onset bipolar disorder?
   (A) Frontal and temporal regions and white matter hyperintensities
   (B) Cerebellum
   (C) Basal ganglia
   (D) Specifically prefrontal cortex
4. Which is the most reliable clinical scale evaluation for psychotic symptoms in bipolar disorder?
   (A) PANSS
   (B) YMRS
   (C) BPRS
   (D) WHO DAS
5. Which is the most important clinical domain among the following for evaluation in the follow-up after the clinical stabilization of the patient?
   (A) Cardiological aspect
   (B) Cognition
   (C) Plasma level
   (D) Endocrinological aspect

References

1. Mintzer J, Targum S. Psychosis in elderly patients: classification and pharmacotherapy. J Geriatr Psychiatry Neurol. 2003;16:199–206.
2. Broadway J, Mintzer J. The many faces of psychosis in the elderly. Curr Opin Psychiatry. 2007;20(6):551–8. [Review]
3. Ostling S, Borjesson-Hanson A, Skoog I. Psychotic symptoms and paranoid ideation in a population-based sample of 95-year-olds. Am J Geriatr Psychiatry. 2007;15:999–1004.
4. Kyomen HH, Whitfield TH. Psychosis in the elderly. Am J Psychiatry. 2009;166(2):146–50.
5. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? Maturitas. 2014;79(2):184–90.
6. Murray PS, Kumar S, Demichele-Sweet MAA, Sweet RA. Psychosis in Alzheimer's disease. Biol Psychiatry. 2014;75(7):542–52.
7. Grau-Rivera O, Gelpi E, Carballido-López E, Sánchez-Valle R, López-Villegas MD. Rapidly progressive dementia with psychotic onset in a patient with the C9ORF72 mutation. Clin Neuropathol. 2015;34(5):294–7.
8. Gossink FT, Vijverberg EG, Krudop W, Scheltens P, Stek ML, Pijnenburg YA, Dols A. Psychosis in behavioral variant frontotemporal dementia. Neuropsychiatr Dis Treat. 2017;13:1099–106.
9. Galimberti D, Dell'Osso B, Altamura AC, Scarpini E. Psychiatric symptoms in frontotemporal dementia: epidemiology, phenotypes, and differential diagnosis. Biol Psychiatry. 2015;78 (10):684–92.
10. Hall D, Finger EC. Psychotic symptoms in frontotemporal dementia. Curr Neurol Neurosci Rep. 2015;15(7):46.
11. Shinagawa S, Nakajima S, Plitman E, Graff-Guerrero A, Mimura M, Nakayama K, Miller BL. Psychosis in frontotemporal dementia. J Alzheimers Dis. 2014;42(2):485–99.
12. Mulsant BH, Ganguli M. Epidemiology and diagnosis of depression in late life. J Clin Psychiatry. 1999;20:9–15.
13. Wohlreich MM, Mallinckrodt CH, Watkin JG, et al. Duloxetine for the long-term management of major depressive disorder in patients aged 65 and older: an open-label study. BMC Geriatr. 2004;4:11.
14. Gournellis R, Lykouras L, Fortos A, Oulis P, Roumbos V, Christodoulou GN. Psychotic (delusional) major depression in late life: a clinical study. Int J Geriatr Psychiatry. 2001;16 (11):1085–91.
15. Kessing L. Differences in diagnostic subtypes among patients with late and early onset of a single depressive episode. Int J Geriatr Psychiatry. 2006;21:1127–31.
16. Heser K, Tebarth F, Wiese B, Eisele M, Bickel H, Köhler M, Mösch E, Weyerer S, Werle J, König HH, Leicht H, Pentzek M, Fuchs A, Riedel-Heller SG, Luppa M, Prokein J, Scherer M, Maier W. Wagner M; age CoDe study group. Age of major depression onset, depressive symptoms, and risk for subsequent dementia: results of the German study on ageing, cognition, and dementia in primary care patients (AgeCoDe). Psychol Med. 2013;43(8):1597–610.
17. Kukreja D, Günther U, Popp J. Delirium in the elderly: current problems with increasing geriatric age. Indian J Med Res. 2015;142(6):655–62.
18. Morandi A, Di Santo SG, Cherubini A, Mossello E, Meagher D, Mazzone A, Bianchetti A, Ferrara N, Ferrari A, Musicco M, Trabucchi M, Bellelli G, ISGoD Group. Clinical features associated with delirium motor subtypes in older inpatients: results of a Multicenter study. Am J Geriatr Psychiatry. 2017;25(10):1064–71.
19. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383:911–22.
20. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227–46.
21. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium and dementia in elderly adults. Lancet Neurol. 2015;14(8):823–32.

22. Gavazzi G, Delerce E, Cambau E, François P, Corroyer B, de Wazières B, Fougère B, Paccalin M, Gaillat J. Diagnostic criteria for urinary tract infection in hospitalized elderly patients over 75 years of age: a multicenter cross-sectional study. Med Mal Infect. 2013;43 (5):189–94.
23. Barthel H, Schroeter ML, Hoffmann KT, Sabri O. PET/MR in dementia and other neurodegenerative diseases. Semin Nucl Med. 2015;45(3):224–33.
24. Linjakumpu T, Hartikainen S, Klaukka T, et al. Use of medications and polypharmacy are increasing among the elderly. J Clin Epidemiol. 2002;55:809–17.
25. Rovera C, Mauri MC, Bertin E, Di Pace C, Paletta S, Reggiori A, De Gaspari IF, Cattaneo D, Mari D, Altamura AC. Duloxetine in elderly major depression disorder: effectiveness and drug plasma level evaluation. Hum Psychopharmacol. 2016;31(5):349–55.
26. Bellivier F, Golmard JL, Rietschel M, Schulze TG, Malafosse A, Preisig M, McKeon P, Mynett-Johnson L, Henry C, Leboyer M. Age at onset in bipolar I affective disorder: further evidence for three subgroups. Am J Psychiatry. 2003;160(5):999–1001.
27. Carlino AR, Stinnett JL, Kim DR. New onset of bipolar disorder in late life. Psychosomatics. 2013 Jan–Feb;54(1):94–7.
28. Besga A, Gonzalez I, Echeburua E, Savio A, Ayerdi B, Chyzhyk D, Madrigal JL, Leza JC, Graña M, Gonzalez-Pinto AM. Discrimination between Alzheimer's disease and late onset bipolar disorder using multivariate analysis. Front Aging Neurosci. 2015;7:231.
29. Hahn C, Lim HK, Lee CU. Neuroimaging findings in late-onset schizophrenia and bipolar disorder. J Geriatr Psychiatry Neurol. 2014;27(1):56–62.
30. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ. 2015;350:h369.
31. Besga A, Chyzhyk D, Gonzalez-Ortega I, Echeveste J, Graña-Lecuona M, Graña M, Gonzalez-Pinto A. White matter tract integrity in Alzheimer's disease vs. late onset bipolar disorder and its correlation with systemic inflammation and oxidative stress biomarkers. Front Aging Neurosci. 2017;9:179.
32. Galimberti D, Prunas C, Paoli RA, Dell'Osso B, Fenoglio C, Villa C, Palazzo C, Cigliobianco M, Camuri G, Serpente M, Scarpini E, Altamura AC. Progranulin gene variability influences the risk for bipolar I disorder, but not bipolar II disorder. Bipolar Disord. 2014a;16 (7):769–72.
33. Galimberti D, Reif A, Dell'Osso B, Palazzo C, Villa C, Fenoglio C, Kittel-Schneider S, Leonhard C, Olmes DG, Serpente M, Paoli RA, Altamura AC, Scarpini E. C9ORF72 hexanucleotide repeat expansion as a rare cause of bipolar disorder. Bipolar Disord. 2014b;16 (4):448–9.
34. Rubino E, Vacca A, Gallone S, Govone F, Zucca M, Gai A, Ferrero P, Fenoglio P, Giordana MT, Rainero I. Late onset bipolar disorder and frontotemporal dementia with mutation in progranulin gene: a case report. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18:1–3.
35. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc. 2002;8(3):448–60.
36. Cheng ST. Cognitive reserve and the prevention of dementia: the role of physical and cognitive activities. Curr Psychiatry Rep. 2016;18(9):85.
37. Goodwin GM, Abbar M, Schlaepfer TE, Grunze H, Licht RW, Bellivier F, Fountoulakis KN, Altamura AC, Pitchot W, Ågren H, Holsboer-Trachsler E, Vieta E. Aripiprazole in patients with bipolar mania and beyond: an update of practical guidance. Curr Med Res Opin. 2011;27 (12):2285–99.
38. Wu CS, Hsieh MH, Tang CH, Chang CJ. Comparative effectiveness of long-acting injectable risperidone vs. long-acting injectable first-generation antipsychotics in bipolar disorder. J Affect Disord. 2016;197:189–95.
39. Kishi T, Oya K, Iwata N. Long-acting injectable antipsychotics for prevention of relapse in bipolar disorder: a systematic review and meta-analyses of randomized controlled trials. Int J Neuropsychopharmacol. 2016;19(9)