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## Managing Antipsychotic Medications in Schizophrenia: Comprehensive Assessment and Personalized Care to Improve Clinical Outcomes and Reduce Costs

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Schizophrenia affects over 26 million individuals worldwide, and it has been listed among the leading 10 causes contributing to the global burden of disease by the World Health Organization.<sup>1</sup> This psychiatric disorder has a tremendous impact on the health status and on the personal and social well-being of the affected individuals. Relative to those without this disease, schizophrenic patients show higher morbidity due to nonpsychiatric illnesses and an increased risk of disability and death.<sup>2</sup>

In the United States, the annual economic expense for schizophrenia has been estimated to be over \$62 billion, with direct medical costs accounting for one-third and indirect costs accounting for half of the overall cost.<sup>3</sup> Direct medical costs include expenses for diagnostic procedures, outpatient and inpatient care, medications, and long-term care. Despite the fact that the largest proportion of costs includes expenses associated with the management of schizophrenia itself, part of the economic resources is directed to the management of morbidity associated with the disease including medical treatments and hospitalizations for associated nonpsychiatric conditions and adverse events of medications. Compared to individuals of the same age without the disease, schizophrenic patients have shown a nearly 2-fold increased risk of cardiovascular disease and diabetes in several studies.<sup>4-6</sup> Schizophrenic patients seem to be susceptible to develop cardiovascular disease. They tend to show impaired glucose tolerance independently of antipsychotic treatment.<sup>7</sup> Frequently, they have an unhealthy lifestyle, including nicotine dependence, alcohol abuse and dependence, substance abuse, physical inactivity, and obesity.<sup>8-10</sup> Schizophrenic patients are chronic users of antipsychotic medications that are known to be associated both with direct adverse effects on the cardiovascular system and with an increased risk of metabolic disturbances including diabetes and weight gain, these associations ultimately determining an increased risk of acute cardiovascular events and death.<sup>11,12</sup> It is well known that schizophrenic patients have higher mortality rates than

nonpsychiatric individuals, and their average life expectancy can be up to 25 years shorter.<sup>6</sup> This excess risk of death seems to be related to both an increased risk of suicide and the associated cardiovascular morbidity.

Schizophrenia is also associated with an additional risk of disability due to comorbid conditions or to the adverse effect of medications. In their article published in the current issue of *The Journal of Clinical Psychiatry*, Wu and colleagues<sup>13</sup> have found that the use of antipsychotic medications may be associated with an increased risk of hip fracture in schizophrenic patients. The risk appeared to be highest in new users of antipsychotics and in those patients treated with conventional agents. These results are in line with what has been already observed in older adults with dementia, in whom use of antipsychotics, and in particular conventional agents, was associated with an increased risk of hip fracture.<sup>14,15</sup> These observational findings disclose a medical issue of high clinical and public health impact occurring in a category of patients who are major consumers of health care resources. Hip fracture is a burdensome event in life and may substantially affect the clinical and functional status of the individual. Hip fracture is associated with an increased risk of adverse consequences such as infections and venous thromboembolism, leading ultimately to increased mortality.<sup>16</sup> This event is also related to increased health care and economic resources utilization since, in most cases, the individual with hip fracture needs to be hospitalized, to be treated with surgery, and to receive rehabilitation care. Recovery from hip fracture to the previous level of functional ability is not always possible, and such condition may be cause of permanent disability and institutionalization.

The mechanisms underlying the suggested increased risk of hip fracture among schizophrenic patients are yet to be understood. Schizophrenic patients may carry an intrinsic risk of fracture due to a certain degree of decreased bone mineral density. There is evidence that high levels of prolactin and cortisol coupled with reduced levels of estradiol and testosterone may mediate the structural abnormalities of the bone in schizophrenic patients.<sup>17</sup> There is evidence that the long-term use of antipsychotic medications is associated with hyperprolactinemia.<sup>18</sup> Prolactin is known to stimulate bone turnover thus contributing to osteoporosis and increasing the risk of hip fracture. Finally, antipsychotic medications may determine an increased risk of fall. Adverse effects such as sedation, gait disturbances due to extrapyramidal syndrome, and orthostatic hypotension contribute to increase the risk of fall in patients treated with antipsychotic medications.

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Schizophrenic patients are also prescribed psychotropic medications other than antipsychotics, such as benzodiazepines, antidepressants, and mood stabilizers. All of these compounds have been associated with an increased risk of fall.<sup>19</sup> Moreover, comorbid conditions such as cardiovascular disease and medications such as  $\beta$ -blockers and diuretics may determine an additional increase in the risk of fall.<sup>20</sup> Lifestyle and environmental factors, such as drug and alcohol consumption, inadequate living arrangement, and lack of social support, may exert a role in increasing the propensity to fall. Finally, it can be postulated that these risk factors may interact in determining falls and consequent hip fractures in patients with schizophrenia. The relative contribution of the above-listed factors to the observed increased risk of fall and hip fracture in schizophrenic patients needs to be disentangled.

The paradigmatic case of hip fracture in schizophrenia points out the complexity of patients affected by this disease who present with an overlap of clinical conditions, syndromes (ie, falls), polypharmacy, and social and functional problems. Given this level of complexity, patients with schizophrenia need a comprehensive assessment before a treatment plan is proposed and medications are prescribed.

Such an assessment may allow for a complete evaluation of patients' conditions and lead to development of a specific and sensible care plan and to the prescription of the most appropriate treatment. Antipsychotics are a heterogeneous group of medications that include numerous compounds, available in several different formulations, with multiple pharmacologic and clinical profiles. Antipsychotics show different risk profiles even within the same class of medications. The individual comprehensive assessment may indeed help the practicing clinician identify those patients

who may be considered at high risk of developing specific treatment side effects. In addition, the comprehensive assessment may lead to the identification of risk factors for a given condition, and this may help in planning preventive interventions. For example, assessment of falls, polypharmacy, reduced physical function, and orthostatic hypotension in schizophrenic patients on antipsychotics may allow the development of interventions that target these conditions and are aimed at reducing the risk of hip fractures.

A therapeutic choice that is based on such assessment, while taking into account the available scientific evidence, is likely to produce benefits in terms of adherence to treatment, clinical outcomes, and reduction of costs. Future studies need to investigate the effectiveness of such approach in the care of patients with schizophrenia.

As the population ages worldwide, an increase in the number of elderly individuals with schizophrenia can be expected. Similar to nonpsychiatric elderly individuals, those with schizophrenia may also present with age-associated cognitive and functional impairment and may be affected by multiple diseases requiring treatment with numerous medications during the day. The number of schizophrenic patients with possible neurodegenerative diseases including Alzheimer's disease and Parkinson's disease is likely to increase in the near future. The prognosis of the psychiatric disease in these patients may be largely influenced by their cognitive and functional performance as well as by the clinical outcomes of medical comorbid conditions. As we have learned from geriatric medicine, these people are those who may benefit most from a comprehensive assessment that drives the therapeutic choice leading to an individual care plan that is tailored to the needs of the affected person.

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