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Letter to the Editor

Polypharmacy in Parkinson's disease: is the risk of sudden death justified?

Dear Editor,

Several studies conducted over a decade have shown an increased risk for polypharmacy and early development of autonomic dysfunction in patients with Parkinson's disease (PD)[1]. However, there is currently little known about the clinical outcome of polypharmacy for people with PD. With these considerations in mind, we read with great interest the elegant article by Giovannini et al[2] evaluating among patients with PD the association between the number of medications and incident hospitalizations. Despite the enormous clinical relevance of this study[2], we also consider it pertinent to evaluate the serious adverse cardiovascular effects mediated by polypharmacy in cases of premature mortality in PD, considered the forefront of medical care in the last years[3].

PD is one of the most common progressive, incurable, and systemic devastating neurodegenerative disorder with high mortality rates when compared to the general population[3]. Specifically, mortality in PD is not increased in the first five years after disease onset, but increases after that, with a relative risk of 3.5 after ten years[3,4]. Therefore, determinant factors such as aspiration pneumonia, cerebrovascular and cardiovascular diseases typically cause deaths in PD patients[3,5]. This being said, sudden unexpected death in PD (SUDPAR) has been considered an important cause of death in PD[3,6]. In a didactic way, SUDPAR has been defined as a sudden death in a patient with PD without any satisfactory explanation of death as determined by autopsy studies[3,6]. Although epidemiological studies are essential to the fight against SUDPAR, important data has shown that an average of 14% of PD individuals die suddenly[3,6]. According to the mechanisms, a combination of cardiac abnormalities is thought to underlie SUDPAR, even because ~60% of PD patients have structural and functional heart changes[3]. The most common risk factors for SUDPAR include age at onset, duration of PD, gender, and motor severity[3,6]. Importantly, polypharmacy has been identified as one of the most significant factors associated with SUDPAR[3,6,7]. In this scenario, several translational studies have found that some pharmacological agents can have serious adverse cardiovascular effects in PD patients, ranging from abnormal heart rate to sudden death[7-12].

Really, some drugs with potential cardiac adverse effects are routinely prescribed in PD[12]. Domperidone, a peripheral dopamine antagonist, is considered the gold standard for treating gastrointestinal symptoms (nausea, vomiting, anorexia, and abdominal bloating) in patients with PD[7,8]. However, it has been indicated that domperidone has limited gastrointestinal benefits and may confer cardiac adverse reactions, ranging from serious ventricular arrhythmias to sudden death[7,8]. In this context, a well-conducted systematic review with meta-analysis endorsed that domperidone intake is associated with an increased risk of fatal events compared to non-use, mainly in older patients using daily doses above 30 mg, including PD patients[8]. In order to translate these findings, our research group verified the effects of the domperidone administration on the cardiac parameters in an animal model of Parkisonism induced by 6-hydroxydopamine (6-OHDA)[9]. In brief, we demonstrated that Parkinson´s rats treated with domperidone showed altered patterns of heart rate, supporting the hypothesis that the use of domperidone may increase the risk of SUDPAR[9]. In parallel, there is strong evidence that antipsychotic drugs used for PD psychosis treatment can cause severe adverse events affecting the cardiovascular system[11,13]. In fact, psychosis is considered a usual disabling nonmotor symptom in PD with a prevalence ranging from 20-70% depending on the stage of the disease[11]. In these lines, several studies indicate adverse cardiovascular effects and even sudden death events in PD individuals exposed to antipsychotic drugs[11,12]. Specifically, it has been clearly shown that antipsychotic drugs exposure is associated with an approximately 1.5-fold increased mortality risk, occurring prominently in patients with PD and those over 65 years old[14].

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On the whole, which lessons did we learn until now? PD is a systemic disease with cases of premature death. Furthermore, as the polypharmacy use increases mortality rates in PD, these drugs should be used with caution, mainly in those individuals who are considered at risk for possible fatal cardiac events. Finally, we absolutely agree that comparative pharmacovigilance analyses can balance measures of PD polypharmacy mortality[15].

Conflict of Interest

The authors declare that they have no conflict of interest.

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