Treatment paradigms in Parkinson's Disease and Covid-19

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Contents

Abstract

People with Parkinson's Disease (PwP) may be at higher risk for complications from the Coronavirus Disease 2019 (Covid-19) due to older age and to the multi-faceted nature of Parkinson's Disease (PD) per se, presenting with a variety of motor and non-motor symptoms. Those on advanced therapies may be particularly vulnerable. Taking the above into consideration, along with the potential multi-systemic impact of Covid-19

on affected patients and the complications of hospitalization, we are providing an evidence-based guidance to ensure a high standard of care for PwP affected by Covid-19 with varying severity of the condition. Adherence to the dopaminergic medication of PwP, without abrupt modifications in dosage and frequency, is of utmost importance, while potential interactions with newly introduced drugs should always be considered. Treating physicians should be cautious to acknowledge and timely address any potential complications, while consultation by a neurologist, preferably with special knowledge on movement disorders, is advised for patients admitted in non-neurological wards. Non-pharmacological approaches, including the patient's mobilization, falls prevention, good sleep hygiene, emotional support, and adequate nutritional and fluid intake, are essential and the role of telemedicine services should be strengthened and encouraged.

1. Introduction

Over the past 2 years the epidemic disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has spread worldwide and profoundly affected the global morbidity and mortality (Abate, Checkol, & Mantefardo, 2021; Piroth et al., 2021). Older age (over 60), along with coexistent comorbidities, were found to increase the risk for severe or critical Coronavirus disease 2019 (Covid-19) (Cascella, Rajnik, Aleem, Dulebohn, & Di Napoli, 2021). More specifically, a large study of confirmed Covid-19 cases reported to the Center for Disease Control and Prevention (CDC) has shown that infected patients are six and 12 times more likely to be hospitalized (45.4 vs 7.6%) or die (19.5 vs 1.6%) respectively, if they have an underlying medical condition, including neurological or neurodevelopmental disabilities, compared to those with an unremarkable medical history (Zhu et al., 2020).

Parkinson's disease (PD) appears with a frequency of 2%–3% among those over the age of 65 and is nowadays acknowledged as the second most common neurodegenerative disorder worldwide (Poewe et al., 2017). Thus, it would not be an uncommon clinical scenario for healthcare professionals to encounter people with PD (PwP) affected with SARS-CoV-2. Through the prism of modern neurology, PD is no longer treated solely as a motor impairment disorder, but affects various systems, exhibiting both motor and non-motor manifestations (Chaudhuri, Healy, & Schapira, 2006). This constellation of symptoms might make the simultaneous management of these two conditions, PD and Covid-19, quite challenging, especially as these patients tend to be admitted in non-neurological wards.

Despite the recent outbreak of SARS-CoV-2, humanity has long been acquainted with the coronavirus (CoV) family with numerous reported outbreaks of CoV species highly pathogenic to humans (Cui, Li, & Shi, 2019). It has been estimated that the percentage of healthy carriers of a CoV strain in the general population is up to 2%, plus these viruses are responsible for about 5-10% of acute respiratory infections in general (Cascella et al., 2021). With these in mind, previous data derived from the management of PwP with respiratory infections or in situations requiring hospitalization, including mechanical ventilation, can prove particularly valuable in the era of the Covid-19 pandemic.

Although PD is more prevalent among the elderly and age might be an aggravating factor in the outcome of Covid-19 patients, no clear associations have been described so far between the two conditions, as the former does not weaken the immune system per se. The difficulty in the management of PwP infected with SARS-CoV-2 lays not only in the nature of PD symptoms, but also in the fact that PwP follow complicated therapeutic schemes, especially in the advanced stages of the disease. Introduction of new drugs, often required in the setting of Covid-19, might predispose to drug-to-drug interactions. Furthermore, the clinical and metabolic changes accompanying Covid-19 might affect the intensity of the parkinsonian symptoms and impose changes in the standard anti-PD treatment. A recent systematic review and meta-analysis showed that the hospitalization and mortality rates among PwP infected with SARS-CoV-2 are 49% and 12% respectively (Khoshnood et al., 2021). Small case series of older PwP with advanced disease state have depicted an even higher mortality rate (40%), especially for those on advanced therapies (50%) due to older age and comorbidities (Antonini, Leta, Teo, & Chaudhuri, 2020), rendering this population particularly vulnerable to the Covid-19 impact.

2. Management of PwP according to Covid-19 severity

According to the National Institute of Health (NIH) there are five categories of Covid-19 severity (Table 1).

Covid-19 usually progresses in two phases (Cascella et al., 2021): an initial early period which coincides or precedes the onset of symptoms when the virus vastly replicates, and a later phase, which is dominated by inflammation induced by cytokines release and activation of the coagulation system, leading to a prothrombotic state. In the former phase, antiviral- and
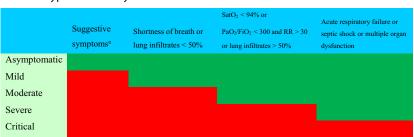
Table 1 Types of severity of Covid-19.

	Suggestive symptoms[a]	Shortness of breath or lung infiltrates < 50%	SatO$_2$ < 94% or PaO$_2$/FiO$_2$ < 300 and RR > 30 or lung infiltrates > 50%	Acute respiratory failure or septic shock or multiple organ dysfunction
Asymptomatic				
Mild				
Moderate				
Severe				
Critical				

[a]Fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, anosmia, dysgeusia.

PaO$_2$/FiO$_2$: ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; RR: respiratory ration (breaths/min); SatO$_2$: oxygen saturation.

antibody-based medication might effectively control the clinical symptoms, while in the later period anti-inflammatory drugs, namely corticosteroids and/or immunomodulating agents, are more efficient.

3. Asymptomatic or mild Covid-19 infection

In asymptomatic or mild Covid-19 infection, no hospital admission is required, and patients are advised to isolate themselves and monitor their symptoms. PwP, especially the elderly, are strongly advised to inform their treating neurologist about their symptoms and be closely monitored until full clinical recovery. Since regular follow-up visits in the Outpatients Clinics have become less frequent (or even completely canceled) during the pandemic due to lockdown regulations imposed by numerous countries, the role of telemedicine has been substantially promoted, covering a wide range of services, such as medical visits, psychotherapy, and physiotherapy, with outcomes comparable to in-person approaches (Cubo, Hassan, Bloem, & Mari, 2020). Although telemedicine services have not been globally applied (some treating physicians would remain in contact with their patients solely via phone calls or emails) (Fasano et al., 2020), such initiatives lay the foundations for future innovations, as the pandemic persists.

3.1 Anti-parkinsonian treatment: Role in Covid-19

It is essential for PwP, not only to adhere to their routine anti-parkinsonian medication during Covid-19, but also to undergo frequent reviews of their regimen, whether they are hospitalized or not, as numerous studies

emphasize that increases in dopaminergic therapy during an infection are often required due to aggravation of motor and non–motor symptoms (Antonini et al., 2020; Cilia et al., 2020). It has been suggested that this aggravation is partly mediated by the subsequent systemic inflammatory response triggered by SARS-CoV-2 (Brugger et al., 2015). Another reason would be the emergence of diarrhea, a common finding among Covid-19 cases (D'Amico, Baumgart, Danese, & Peyrin-Biroulet, 2020), which might exert a devastating effect on the pharmacokinetics of orally administered anti–parkinsonian medications, especially levodopa, leading to reduced absorption of the drug and, thus, an increased frequency and duration of OFF episodes (Cilia et al., 2020).

Recent evidence has suggested that some anti–parkinsonian medication might play a beneficial role in the pathophysiology of Covid-19. A potential protective role of dopamine has been suggested, as a dopamine D1 receptor agonist was found to suppress endotoxin–induced pulmonary inflammation in mice (Bone, Liu, Pittet, & Zmijewski, 2017). On the other hand, L–Dopa decarboxylase (DDC), an essential enzyme in the biosynthesis of both dopamine and serotonin, seems to be the most significantly co-expressed and co-regulated gene with Angiotensin-Converting Enzyme 2 (ACE2) in non-neuronal cell types, thus, affecting the dopamine blood levels (Nataf, 2020). ACE2 has been identified as a major cell entry receptor for SARS-CoV-2 (Zhang, Penninger, Li, Zhong, & Slutsky, 2020), while levodopa in PwP is always administered with a DDC inhibitor, such as car-bidopa or benserazide, to prevent levodopa from peripherally converting to dopamine. Researchers showed that DDC levels rose in asymptomatic or mild severity Covid-19 patients, while an inverse relationship was noted between SARS-CoV-2 RNA levels and DDC expression, leading them to assume a detrimental effect of DDC inhibitors on Covid-19 course (Fasano et al., 2020; Mpekoulis et al., 2021). Amantadine, a drug with mild anti–parkinsonian properties, which is classically used to manage dyskinesias in PD, has been found to exhibit anti–viral properties, while growing evidence has shown that its use might mitigate, or even prevent, the effects of Covid-19 (Abreu, Aguilar, Covarrubias, & Durán, 2020; Cortés–Borra & Aranda–Abreu, 2021; Kamel et al., 2021). Finally, an analysis of SARS-CoV-2 and human proteins revealed the Catechol-O-methyltransferase (COMT) inhibitor entacapone as a potential antiviral therapeutic agent against SARS-CoV-2 (Gordon et al., 2020). Despite the above findings, Fasano and colleagues, who conducted a multi-center study using a cohort of PwP with Covid-19, commented that no clear associations have arisen

between anti-parkinsonian drugs and Covid-19 outcome, although larger cohorts are needed to further explore such effects (Fasano, Elia, et al., 2020).

3.1.1 Potential complications from disruptions in dopaminergic treatment

According to a survey conducted by the Movement Disorders Society (MDS) Epidemiology group, 45.4% of PwP worldwide encountered difficulties getting their regular prescriptions for dopamine replacement therapy during the pandemic with more devastating effects observed in lower income countries (Cheong et al., 2020). An abrupt cessation or a significant reduction of anti-parkinsonian medication might predispose to the so-called parkinsonism-hyperpyrexia syndrome, a rare, but life-threatening condition, caused by acute deficiency of iatrogenic dopamine, which presents with hyperthermia, severe rigidity, impaired consciousness, stupor, autonomic dysfunction (including respiratory failure) and high serum creatinine kinase levels (Newman, Grosset, & Kennedy, 2009). It might also be precipitated by respiratory, gastrointestinal or urinary infections (Simonet, Tolosa, Camara, & Valldeoriola, 2020). Parkinsonism-hyperpyrexia syndrome is the modern term, referring to the previously used "neuroleptic malignant-like syndrome." It is an urgent condition, requiring hospitalization, occasionally in the Intensive Care Unit (ICU), supportive care, intravenous fluids and, most importantly, that the patient resumes dopaminergic treatment as soon as possible, although symptoms might be resistant to levodopa (Newman et al., 2009; Serrano-Dueñas, 2003). If treatment with levodopa fails, administration of subcutaneous apomorphine or transdermal rotigotine or intravenous amantadine, if available, might be of use (Simonet et al., 2020). A pulse steroid trial could also be used, although evidence on effectiveness is scarce (Clarke, 2004). Administration of dantrolene sodium and intragastric bromocriptine have also been reported in the literature as useful treatment options (Takubo et al., 2003). Parkinsonism-hyperpyrexia syndrome has a mortality rate of up to 4%, but about 30% of patients are left with permanent deficits (Newman et al., 2009).

Abrupt cessation or even tapering of dopamine agonists might lead to dopamine agonist withdrawal syndrome, which is characterized by prominent psychiatric features (anxiety, agitation, panic attacks, depression, suicidal ideation), dysautonomia and generalized pain. Symptoms are often refractory to levodopa and psychotropic medication and respond to resuming dopamine agonists therapy (Chaudhuri et al., 2015; Nirenberg, 2013).

Symptoms might be self-limited, although the severity varies greatly among different patients, with higher daily doses of dopamine agonists and total dose of dopaminergic medication being the most significant risk factors (Yu & Fernandez, 2017).

In case of worsening of parkinsonism, PwP should contact their treating neurologist for an urgent consultation. The above syndromes are severe, although rare. Aggravation of symptoms might be attributed to the natural course of PD per se, especially if patients have not visited their treating neurologist for a while. Covid-19 could also contribute to aggravation of both motor and non-motor PD symptoms (Fearon & Fasano, 2021). Finally, other metabolic causes, like electrolyte imbalances or co-infections, should be excluded (Brugger et al., 2015).

3.1.2 Management of advanced therapies in PD and Covid-19

As far as PD advanced therapies are concerned, management of Deep Brain Stimulation (DBS) parameters might be particularly challenging during the pandemic. Minor changes can be implemented by patients or caregivers themselves, following instructions through telemedicine services or phone consultations (Miocinovic et al., 2020; Sharma et al., 2021). It should be emphasized to both patients and caregivers to pay close attention to the battery status of non-rechargeable stimulators, and to ensure that rechargeable stimulators are always kept charged. Potential cessation of DBS functioning might lead to the rare, but life-threatening situation of DBS-withdrawal syndrome, characterized by a severe akinetic crisis, which might not respond to dopamine replacement therapy (Reuter et al., 2018). Those with a PD diagnosis for more than 15 years, who are efficiently managed with bilateral subthalamic nuclei stimulation are more at risk of developing this urgent condition (Cartella, Terranova, Rizzo, Quartarone, & Girlanda, 2021). Infections of the DBS hardware might also lead to disruption of treatment (Reuter et al., 2018). Patients should be instructed by their treating neurologist to always keep a stock of orally administered levodopa to substitute for any unexpected DBS malfunctioning. If patients notice any worsening of their PD symptoms, they should immediately contact their treating neurologist and get proper instructions, as decision making under these circumstances is personalized for each case, depending on the severity of symptoms, the battery status and the patient's tolerance to a potential DBS interruption (Miocinovic et al., 2020). Subjacent metabolic causes should also be excluded. Even during the pandemic, there is still room for urgent procedures, if the patient's safety due to DBS malfunction

is compromised. In case of new, non-urgent DBS implementations, delays might be expected, although such interventions are still scheduled with respect to the different countries healthcare system regulations with priority given to the most debilitated patients (Siddiqui et al., 2021).

Dose adjustments in PwP under infusion therapies might also be challenging, as patients might be asked to make such modifications by themselves under the remote guidance of their treating neurologist, assuming that the pump is set in the non-locked mode. The role of an attentive carer is extremely valuable under these circumstances, as patients' manual dexterity or cognitive performance might be impaired. Video consultations could help the treating neurologists get a more objective evaluation of the clinical status of the patient in these circumstances. However, such evaluations are often conducted through phone calls, posing risks for the aptness of dose changes. Furthermore, allowing patients such an access to dose modifications might render them vulnerable at presenting with dopamine dysregulation syndrome, especially if they use an apomorphine pump or have a history of impulse control disorders (ICDs) (Fasano, Antonini, et al., 2020). In case patients are not properly educated to make such adjustments themselves, some pump manufacturers provide the possibility of a specialized nurse to make home visits, depending on the geography of the patient's residency, following strictly defined safety protocols (Fasano, Antonini, et al., 2020). Manufacturers can also ship new equipment to replace the hardware of the pump in case of damage. It is very important for patients under infusion therapies to be instructed to keep a stock of orally administered levodopa (preferably dispersible or liquid formulations of levodopa) for "rescue" therapy, should this be required in case of pump malfunction or failure due to the emergent risk of parkinsonism-hyperpyrexia syndrome (Cartella et al., 2021). In case of PD symptoms worsening, patients should contact their treating neurologist, as personalized arrangements might be needed. Catheter blockage is a common cause of pump malfunction and can be usually managed by the patient or caregiver without further complications. Subjacent metabolic causes, including skin or hardware or *Helicobacter pylori* infections, or other gastrointestinal complications, like a peptic ulcer, should be excluded (Fasano, Antonini, et al., 2020; Tan et al., 2015). Delays in placement of new infusion therapies are to be expected during the pandemic, although the majority of these procedures are eventually scheduled in due time according to the different healthcare systems regulations and safety protocols and with priority given to more frail patients (Richter et al., 2021).

3.2 Pharmacological therapy in Covid-19 and potential complications in PwP

3.2.1 Monoclonal antibodies

According to NIH guidelines, SARS-CoV-2 neutralizing monoclonal antibodies, such as REGN_COV2 (casirivimab and imdevimab) or bamlanivimab/etesevimab or sotrovimab can be considered for outpatients with mild severity of Covid-19, who are thought to be at risk of disease progression with a low threshold for hospitalization (Cascella et al., 2021), especially for those over 65 years old (Nathan et al., 2021; Weinreich et al., 2021). No absolute contraindications have been reported for the above medications and they could be safely administered to PwP weighing over 40 kg (Gupta et al., 2021; Nathan et al., 2021; Weinreich et al., 2021). NIH recommends against the administration of dexamethasone at this stage (Cascella et al., 2021).

3.2.2 Common cold medications

There have been reports about people who tend to self-medicate with easily accessible analgesics and drugs used to relieve common cold symptoms, some of them sold over the counter (Quincho-Lopez, Benites-Ibarra, Hilario-Gomez, Quijano-Escate, & Taype-Rondan, 2021). Concomitant administration of selective monoamine oxidase (MAO) inhibitors, such as selegiline and rasagiline, with sympathomimetic substances, such as those used to relieve nasal congestion and other rhinitis symptoms (e.g., budesonide, triamcinolone and xylometazoline), might lead to hypertensive crisis. Other common cold medication, like ephedrine, pseudoephedrine, and dextromethorphan, increase the possibility of serotonin syndrome when co-administered with MAO inhibitors, as both drug categories raise serotonin levels. PwP should be properly and timely informed by their treating neurologist that co-administration of the above medication is strictly contraindicated or consult their pharmacist before purchasing such products. Occurrence of serotonin syndrome might be even more likely in patients who are treated simultaneously with both MAO inhibitors and selective serotonin reuptake inhibitors (SSRIs), as depression is, indeed, a prevalent condition among PwP, commonly treated with SSRIs (Seppi et al., 2019). This combination is usually well-tolerated; however, cases of serotonin syndrome have been described in the literature (Aboukarr & Giudice, 2018), therefore, extra caution is needed. Serotonin syndrome, a potentially life-threatening condition, bears similarities to the neuroleptic malignant syndrome, but, apart from agitation and confusion, it is characterized by a

mixture of neuromuscular abnormalities (akathisia, tremor, myoclonus, hyperreflexia, rigidity) and autonomic hyperactivity (Volpi–Abadie, Kaye, & Kaye, 2013). Symptoms usually appear acutely, about 6–12 h after the introduction or the dose increase of the causative agent (Simonet et al., 2020). It is a diagnosis of exclusion and it is of the utmost importance to early identify and withhold any drugs that might contribute to the hyper-serotonergic situation, while supportive care needs to be promptly provided (Volpi–Abadie et al., 2013). Non-selective serotonin receptor antagonists, like cyproheptadine and methysergide, might also be of help (Simonet et al., 2020). Under these circumstances, the temporary and prophylactic cessation of MAO inhibitors is advised. These do not necessarily need to be replaced by other antiparkinsonian drugs; however, if such need arises, amantadine could be a reasonable option. Amantadine is assumed to both block dopamine reuptake in presynaptic vesicles and increase dopamine release, therefore imitating the action of MAO inhibitors, which reduce dopamine metabolism and prolong dopamine availability in the synaptic cleft. An alternative option in case of sub-treatment would be an up–titration of the total levodopa dose.

4. Moderate Covid-19 infection

4.1 Hospitalization in PwP with Covid-19 and potential complications

Patients with clinically moderate Covid-19 are usually admitted to the hospital for closer monitoring, especially if other comorbidities are present (Cascella et al., 2021). There have been numerous reports describing the dissatisfaction of PwP and their caregivers in relation to the care received during hospitalization. Most complaints refer to delays, or even omissions in their regular anti-parkinsonian regimen, leading to worsening of motor performance, increased rate of falls and longer admission periods due to complications, such as co-infections (Buetow, Henshaw, Bryant, & O'Sullivan, 2010; Gerlach, Broen, van Domburg, Vermeij, & Weber, 2012; Magdalinou, Martin, & Kessel, 2007).

There is a sub-population of almost 40% among PwP with respiratory dysfunction in the absence of lung or cardiovascular disease (Baille et al., 2019). Respiratory abnormalities in PD, including both upper and lower obstructive or restrictive patterns, have been well–recognized, and attributed to dysautonomia, camptocormia and kyphoscoliosis (Arrigo et al., 2020). An impaired brainstem ventilatory control might also contribute to the

respiratory dysfunction, even in premotor stages of PD, affecting the central drive of breathing (Vijayan, Singh, Ghosh, Stell, & Mastaglia, 2020). Since a number of studies have found that respiratory impairment might worsen during OFF periods, most researchers strongly support the protective role of anti-parkinsonian medication against respiratory failure (Arrigo et al., 2020). It is, thus, of the utmost importance for PwP to receive their medication in an appropriate and timely manner, especially in the advanced stage of the disease, when patients usually follow complicated and personalized treatment schemes. Consulting neurologists should highlight this necessity when PwP with Covid-19 are admitted in non-neurological wards. A detailed and thorough medical history should be taken by treating physicians prior to admission, so that the personnel who is unfamiliar with PD understands the significance of adhering to defined dose intervals. Under special circumstances, patients could be allowed to receive their medications by themselves. Special caution is advised when considering the use of anticholinergic drugs in PwP, which are commonly used for obstructive pulmonary disorders, as they have been associated with cognitive impairment and delirium, especially in advanced stages of PD, when cognition might be already compromised (Arrigo et al., 2020).

4.2 Pharmacological therapy in Covid-19 and potential complications in PwP

4.2.1 Dexamethasone

Dexamethasone remains the cornerstone of treatment for Covid-19 patients who require hospitalization, either alone or in combination with remdesivir (Cascella et al., 2021). Administration of dexamethasone is not contraindicated for PwP, although special care should be taken to avoid any adverse events. Since an inflammatory component has long been presumed in the pathogenesis of PD (Tufekci, Meuwissen, Genc, & Genc, 2012), dexamethasone was found to exert a protective effect on dopamine neurons and was associated with a better motor performance in experimental parkinsonian mice models (Joshi & Singh, 2018; Tentillier et al., 2016).

The use of corticosteroids has been connected to a potential neuropsychiatric impairment with about 2-60% of patients presenting with mood swings, depression, mania, suicidality, anxiety, confusion, and behavior changes, along with impairment of their sleep pattern (Chen et al., 2021; Dubovsky, Arvikar, Stern, & Axelrod, 2012; Noreen, Maqbool, & Madni, 2021). The term "steroid psychosis," which is often used in the literature to describe such phenomena, is considered by many rather misleading,

as neuropsychiatric impairment exhibits a vast diversity of symptoms. In about 6% of patients who receive steroids, the neuropsychiatric effects are expected to be rather severe with high doses considered as the most significant precipitating factor (Dubovsky et al., 2012). The use of dexamethasone in critically ill patients was also found to aggravate the occurrence of delirium (Wu, Li, Liao, & Wang, 2021).

In PwP, anxiety, psychosis and clinically significant depression are encountered in up to 60%, 40% and 35% respectively (Schapira, Chaudhuri, & Jenner, 2017). It is therefore of particular importance to differentiate whether such symptoms might be steroid-induced or merely exacerbations of non-motor symptoms of PD. If such phenomena occur during OFF periods, it is preferable to adjust the anti-parkinsonian regimen before introducing any further modifications. It is also crucial to exclude other potential metabolic causes, such as electrolyte imbalances, hypo- or hyperglycemia, intoxication, side effects of other medications or additional infections (Janes, Kuster, Goldson, & Forjuoh, 2019). SARS-CoV-2 infection per se may exacerbate or trigger psychiatric symptoms, even in the absence of steroidal treatment, most of which are self-remitting (Ferrando et al., 2020; Varatharaj et al., 2020). In a large meta-analysis from Asia, North America and Europe, steroid-induced mania and psychosis were only reported in 13 (0.7%) of 1744 cases in the acute stage, although other neuropsychiatric symptoms, like confusion, depression, anxiety, impaired memory and insomnia were quite common, all of them presenting in more than 30% of inflicted patients (Rogers et al., 2020).

Dexamethasone has a 36- to 72-h period of action and neuropsychiatric symptoms usually appear within 2 weeks after administration; a subacute onset of up to 12 weeks has also been described (Wada et al., 2001). No evidence-based guidelines are available concerning the treatment of corticosteroid-induced neuropsychiatric impairment, as most information is based on case reports and case series. However, such phenomena are expected to typically resolve in more than 90% of cases with corticosteroids tapering at a dose of less than the equivalent of 40 mg/day of prednisone and, eventually, with the complete cessation of steroids (Dubovsky et al., 2012; Warrington & Bostwick, 2006). In most cases, any associated delirium commonly resolves within days and psychosis within a week, though depression or manic symptoms may last up to 6 weeks after discontinuation of steroids (Janes et al., 2019).

Treating physicians need to be vigilant in identifying such phenomena, as treatment modifications might be required in PwP, while corticosteroids

tapering might not be an option, especially in more severe cases of Covid-19. Dopamine agonists might need to be gradually discontinued if psychotic features appear and replaced with the equivalent dose of levodopa. In patients with mania, several publications support the efficient use of carbamazepine, valproate, lamotrigine, and phenytoin as mood stabilizers (Dubovsky et al., 2012; Wada et al., 2001). For PwP treated with pergolide, the use of valproate and phenytoin is contraindicated, as these drugs compete for protein-binding sites resulting in toxic concentrations of either or both of them (Dalvi & Ford, 1998). Moreover, the use of carbamazepine should be avoided in PwP receiving clozapine, as concomitant administration might lead to development of neuroleptic malignant syndrome (Dalvi & Ford, 1998). To timely address manic symptoms, antipsychotics can be co-administered or given alone. Although phenothiazines, butyrophenones and zotepine have been effectively used in steroid psychosis (many support that a good therapeutic response to low doses of haloperidol or olanzapine constitutes a characteristic of corticosteroid-induced psychosis (Wada et al., 2001)), these drugs are not suitable for PwP, as they tend to exacerbate parkinsonian symptoms. The only antipsychotics that can be safely used with appropriate monitoring in PwP are clozapine, quetiapine and pimavanserin (Seppi et al., 2019), although no reports on their effects on corticosteroids-induced psychosis are currently available.

Previous reports suggested that antidepressants, like tricyclic antidepressants (TCAs), should be avoided in steroid psychosis, partly due to their anticholinergic effects which might exacerbate delirium. However, newer data suggests that the indication for antidepressants should be re-examined (Wada et al., 2001), as fluoxetine, sertraline and venlafaxine have been successfully used in various case reports (Dubovsky et al., 2012). Fluoxetine, in particular, has been shown to be a promising drug in the context of Covid-19 due to reported anti-inflammatory properties (Dąbrowska, Galińska-Skok, & Waszkiewicz, 2021). TCAs like nortriptyline and desipramine have been labeled as "likely efficacious" and "clinically useful" to treat depression in PwP (Seppi et al., 2019) and could be considered also for anxiety in PD, although they should be avoided in patients with suicidal ideation or cardiovascular problems (Prediger, Matheus, Schwarzbold, Lima, & Vital, 2012). Venlafaxine is considered 'efficacious' and 'clinically useful' in alleviating depressive symptoms in PD (Seppi et al., 2019). Its role in relieving anxiety symptoms is controversial and it should be avoided in patients with cardiac disease, electrolyte imbalance and hypertension (Prediger et al., 2012), all of which are often encountered

in the Covid-19 setting (Azer, 2020). Fluoxetine and sertraline are thought to be 'possibly clinically useful' in treating depression in PD (Seppi et al., 2019), although their role in anxiety is also controversial and some clinicians prefer them only when depression is also present (Prediger et al., 2012). Benzodiazepines do not constitute a good therapeutic option for anxiety in PD, especially in the elderly, as they have been associated with sedation, cognitive impairment, confusion and falls, while the risk of abuse and dependence, as well as the possibility of withdrawal syndrome, should be considered (Prediger et al., 2012).

4.2.2 Remdesivir

Remdesivir, a broad-spectrum anti-viral agent, along with dexamethasone, might be considered for patients who require supplemental oxygen (Cascella et al., 2021), although evidence is conflicting (Pan et al., 2021). Remdesivir is administered intravenously at a weight-based dose (5- or 10-day scheme) and has been approved for adults weighing a minimum of 40 kg (Aleem & Kothadia, 2021). Although there is evidence that it inhibits numerous cytochrome P450 (CYP450) enzymes in vitro, no such indications have arisen in vivo, as there are no reports of severe drug-to-drug interactions up to now, and it is generally considered a well-tolerated treatment (Aleem & Kothadia, 2021). Remdesivir can be safely administered to PwP, as no interactions with anti-parkinsonian medications have been reported up to now, although the pharmacokinetics of the drug have not been extensively studied for those over 65 years old. PwP and their treating physician need to by particularly alert to potential adverse events of the drug, including hypotension, arrhythmias, nausea and vomiting, constipation and gastroparesis (Aleem & Kothadia, 2021), as dysautonomia might be a prominent feature in PwP (Chaudhuri, 2021). Close monitoring with a holistic approach to the patients' symptoms is advised.

4.2.3 Prophylactic thromboembolic agents

Thromboembolic prophylaxis with appropriate anticoagulation is also indicated in moderate Covid-19 (Cascella et al., 2021). Anticoagulation of any kind does not constitute a contraindication in PwP, even in those with advanced therapies, including DBS or infusion therapies.

4.2.4 Antibiotics

In case of a potential bacterial co-infection in Covid-19 patients, empirical antibiotic treatment should be initiated (Cascella et al., 2021). For PwP, in

particular, increased awareness is advised, as they might present with swallowing difficulties, especially in advanced stages (Suttrup & Warnecke, 2016), while the cough reflex might be impaired, even from the early stages of the disease, rendering the removal of secretions problematic (Ebihara et al., 2003) and predisposing to aspiration pneumonia, one of the leading death causes among PwP (Won, Byun, Oh, Park, & Seo, 2021).

Considering the choice of antibiotics, most physicians adhere to local community-acquired pneumonia guidelines (Bendala Estrada et al., 2021). In a meta-analysis of 13,932 Covid-19 patients, beta-lactams, especially third-generation cephalosporines, were the most commonly administered agents (72.0%), followed by macrolides (60.2%) and fluoroquinolones (13.3%) (Bendala Estrada et al., 2021). In a different meta-analysis of 375 patients, fluoroquinolones were the most commonly used antibiotics (56.8%), followed by ceftriaxone (39.5%) and azithromycin (29.1%) (Chedid et al., 2021). Other broad-spectrum antibiotics, like linezolid, have also been used (Miranda et al., 2020). In a large meta-analysis of 3338 Covid-19 patients, bacterial co-infection and secondary infection were identified in 3.5% and 14.3% of them respectively, though the majority of patients (71.8%) did receive antibiotics (Langford et al., 2020). Although most antibiotics are generally well-tolerated by patients, including those with PD, the general rule is that physicians should weigh benefits and potential risks and be extra-cautious to avoid initiating such medications when unnecessary. Early de-escalation of empirical antibiotic treatment is strongly encouraged, as longer treatments might predispose to development of antimicrobial resistance and opportunistic pathogens superinfections, which are associated with increased morbidity and mortality in vulnerable Covid-19 patients (Chedid et al., 2021).

In regard to antibiotics used in PwP, there have been reports about potential neuroprotective effects in PD animal models (Yadav, Thakur, Shekhar, & Ayushi., 2021), with ceftriaxone found to offer several advantages in improving clinical aspects of parkinsonism due to a long-term upregulation of glutamate transporter GLT-1 and removal of synaptic glutamate (Kelsey & Neville, 2014). On the other hand, a significantly increased PD prevalence was found among patients using narrow-spectrum penicillin and penicillinase-resistant penicillin, which was attributed to gut microbial imbalance (dysbiosis) in PwP and inflammation, promoted by consumption of antibiotics (Ternák, Kuti, & Kovács, 2020). Since alterations in the gut microbiome of PwP have been confirmed (Romano et al., 2021) and recent studies suggest that patients with altered gut microbiota might experience

more severe Covid-19 symptoms (Kim, 2021), empirical treatment for bacterial pneumonia in PwP should only be initiated when clinical suspicion is high.

Most antibiotics carry a significant risk of typical gastrointestinal adverse events, like nausea, vomiting, abdominal pain and diarrhea, especially macrolides and quinolones (Patel & Hashmi, 2021; Yan & Bryant, 2021). PwP should be made aware of such side effects, as these symptoms might overlap with typical non-motor symptoms of PD or interfere with the absorption of orally administered parkinsonian medication. Treating physicians should also be aware that third-generation cephalosporines, and more commonly quinolones, have been associated with a risk of pseudomembranous colitis triggered by *Clostridium difficile* in order to timely differentiate and treat this condition in PwP (Arumugham, Gujarathi, & Cascella, 2021; Yan & Bryant, 2021).

Third-generation cephalosporines have known neurotoxic effects, including epileptogenic activity, new-onset movement disorders (asterixis, myoclonus) and encephalopathy characterized by limb numbness or weakness, behavior impairment and cognitive deficits. Symptoms typically present acutely within 1 week of antibiotic therapy initiation and subside within 1 week after treatment cessation (Arumugham et al., 2021).

Macrolides had been widely used in Covid-19 treatment during the first months of the pandemic due to their antiviral features (Bendala Estrada et al., 2021). Initial studies had shown that azithromycin, either alone or in combination with hydroxychloroquine, was effective against SARS-CoV-2 (Gautret et al., 2020; Touret et al., 2020), while macrolides use was associated to a higher survival ratio in Covid-19 patients (Bendala Estrada et al., 2021). Although generally well-tolerated, macrolides exhibit a variety of side effects which are particularly relevant for PwP. More specifically, they have been associated with QT interval prolongation in the cardiac cycle, predisposing to ventricular tachycardia, ventricular fibrillation and Torsades de Pointes syndrome, which are severe, life-threatening arrhythmias, especially in the presence of electrolyte abnormalities, like hypokalemia (Patel & Hashmi, 2021). Many anti-parkinsonian drugs, including apomorphine or medication commonly used in PD comorbidities, like antidepressants (citalopram, escitalopram, venlafaxine, nortriptyline) or antipsychotics (quetiapine, clozapine), have also been linked to QT prolongation (Tisdale, 2016). Thus, concomitant use of macrolides is not recommended for these patients. If macrolides administration is deemed necessary, electrolytes blood levels, including calcium, potassium and

magnesium, should be measured and the patient should be carefully monitored with serial electrocardiograms (ECG), while the treating physicians should also consider cessation of the interacting agents (Patel & Hashmi, 2021). Patients using apomorphine, either as a pen or as a pump, might need to discontinue this medication before introducing macrolides. While apomorphine injections can be abruptly discontinued, the apomorphine pump infusion needs to be gradually withdrawn. In the former case, extra doses of levodopa could substitute the apomorphine shots in order to manage morning or unexpected OFF state. Replacement of an apomorphine pump with the levodopa equivalent dose can be more challenging, as gradually increasing doses of multiple levodopa administrations will be needed, following a personalized scheme and a close follow-up of the patient. The same principles apply to quinolones, which have also been associated with QT interval prolongation (Yan & Bryant, 2021).

Macrolides are also thought to inhibit the liver metabolism of bromocriptine, thus leading to accumulation of the drug and manifestation of ergotism (Dalvi & Ford, 1998). Moreover, the macrolide spiramycin might form a non–absorbable complex with carbidopa, which affects the pharmacokinetics of levodopa when the two compounds are co-administered (Dalvi & Ford, 1998).

Arthralgias are commonly encountered in patients treated with quinolones and self-resolve after treatment cessation (Yan & Bryant, 2021). Pain in PD is a prominent non–motor feature (Schapira et al., 2017), which might affect a patient's mobility, thus, such side effects might cause extra discomfort in a PwP. Moreover, tendon rupture, another typical side effect of quinolones, is more common among people over the age of 60 and might also jeopardize the vulnerable mobility of PwP (Yan & Bryant, 2021). Since the quinolone ciprofloxacin strongly inhibits CYP1A2, it may increase the bioavailability of ropinirole (Kaye & Nicholls, 2000). Although their co-administration was found well-tolerated in vivo, treating physicians should consider a dosage adjustment in PwP treated with ropinirole, if ciprofloxacin is initiated (Kaye & Nicholls, 2000).

Linezolid is considered a broad spectrum antibiotic with a reversible MAO inhibitor potential (Quinn & Stern, 2009). Concomitant use of linezolid and serotonergic agents (SSRIs, serotonin, and norepinephrine reuptake inhibitors (SNRIs), TCAs, rasagiline/selegiline, bromocriptine) is contraindicated. If linezolid is to be administered, it is recommended that the serotonergic drug is discontinued with a washout period of at least 2 weeks, while monitoring the patient for development of serotonin

syndrome (Hisham, Sivakumar, Nandakumar, & Lakshmikanthcharan, 2016). Although no specific case reports have been published about serotonin syndrome among patients treated with linezolid and levodopa–carbidopa this combination should also be avoided (Pettit et al., 2016).

5. Severe Covid-19 infection

5.1 Pharmacological therapy in Covid-19 and potential complications in PwP

Patients with severe Covid-19 need to be hospitalized. The same principles mentioned above for prophylactic anticoagulation and empiric antibiotic treatment in case of bacterial infection also apply for severe Covid-19. A stronger indication for dexamethasone administration applies on such cases, usually in combination with remdesivir or baricitinib or tocilizumab, if patients require oxygen supplementation with high flow nasal cannula (HFNC) or non-invasive ventilation (Cascella et al., 2021). In case dexamethasone is contraindicated, the combination of baricitinib plus remdesivir can be of use (Cascella et al., 2021).

5.1.1 Baricitinib

Baricitinib is a Janus kinase (JAK) inhibitor, which can be used in combination with remdesivir or dexamethasone (Cascella et al., 2021). Although it bears a small risk of thromboembolic events and secondary infections, it is unlikely to cause any serious complications when administered for short time periods like in the Covid-19 setting (Hsu, Mao, Liu, & Lai, 2021). Baricitinib can be safely administered to PwP with severe Covid-19, and no drug-to-drug interactions have been described with antiparkinsonian medication.

5.1.2 Tocilizumab

Tocilizumab is an anti-interleukin (IL)-6 receptor alpha monoclonal antibody, which is effectively used in Covid-19 patients who manifest rapid respiratory deterioration (Cascella et al., 2021). Although a number of adverse events have been reported to be associated with tocilizumab use, it has not been associated with any known serious drug-to-drug interactions or any contraindications for PwP (Hsu et al., 2021). Caution is advised with concurrent use of myelotoxic medication or immunosuppressive drugs due to the risk of toxicity or secondary infections respectively (Hsu et al., 2021).

5.1.3 Norepinephrine

Norepinephrine is a first-line vasopressor aiming to maintain a mean arterial pressure of 60–65 mmHg in cases of critically ill Covid-19 patients with hypotension that do not respond to volume resuscitation with intravenous administration of fluids (Cascella et al., 2021; Smith & Maani, 2021). There are no absolute contraindications in norepinephrine use (Smith & Maani, 2021). Special caution is advised for patients who are treated with MAO inhibitors or those on amitriptyline or imipramine-type antidepressants, which might be the case in PwP, as this combination might lead to resistant hypertension (Smith & Maani, 2021).

5.1.4 Plasma transfusion

Food and Drug Administration (FDA) has approved the use of convalescent plasma in patients with severe life-threatening Covid-19, although reported results are mixed (Cascella et al., 2021). There are no known contraindications for plasma transfusion in PwP or interactions with anti–parkinsonian medication (Liumbruno et al., 2009).

5.2 Intubation, ICU admission, and potential complications in PwP and Covid-19

In severe Covid-19 cases, intubation and mechanical ventilation, along with further support of the patient in the ICU, might be deemed necessary. The published evidence commenting on the duration of ICU admission and ventilation among Covid-19 patients with and without PD are conflicting, with a large German study supporting that figures did not significantly differ between the two populations (Huber et al., 2021), while others found opposite results (Zhang, Schultz, Aldridge, Simmering, & Narayanan, 2020). In case of prolonged endotracheal intubation, it is preferable to proceed early in performing a tracheostomy (Gerlach, Winogrodzka, & Weber, 2011).

Adhering to the established dopaminergic medications dosing scheme in intubated PwP with Covid-19 is particularly important to prevent the development of rigidity with contractures and impairment of the respiratory function with low vital capacity and peak expiratory flow and aggravation of PD symptoms (Fasano, Antonini, et al., 2020). Discontinuation of dopaminergic medication in ICU might result in chest wall rigidity, thus impairing the ventilator management (Freeman et al., 2007). Interestingly, levodopa has been found to strengthen diaphragm contraction in anesthetized dogs and patients with chronic obstructive pulmonary disease (COPD) and acute respiratory dysfunction (Aubier et al., 1989; Fujii, 2006). Maintaining the

standard regimen would also lower the risk of parkinsonism–hyperpyrexia syndrome in case of abrupt cessation or decrease in levodopa equivalent dose; insertion of a nasogastric tube is highly recommended to allow administration of antiparkinsonian medication (Roberts & Lewis, 2018). Of note, enteral nutrition with high protein-enriched supplements, commonly used in the ICU, was found to constitute an independent risk factor for parkinsonism–hyperpyrexia syndrome, as dietary protein might compromise the absorption of levodopa (Bonnici, Ruiner, St-Laurent, & Hornstein, 2010). Proper levodopa dosing is also expected to minimize the risk of rigidity and distress on emergence of anesthesia (Roberts & Lewis, 2018). For PwP under infusion therapies, it is advised for these therapies to be continued (Fasano, Antonini, et al., 2020). Alternatively, the levodopa equivalent dose could be orally administered, although it would be better if infusion therapies were not abruptly discontinued. If required, the levodopa tablets can be administered in a crushed form through a nasogastric tube to achieve faster absorption and action, or identical doses of a soluble levodopa preparation can be used. Replacement of an apomorphine pump with the levodopa equivalent dose can be challenging, as gradually increasing doses of multiple levodopa administrations will be needed, following a personalized scheme and a close follow-up of the PwP. However, if the oral administration of levodopa is not feasible for any reason, subcutaneous administration of apomorphine is recommended, even in PwP without any prior exposure to apomorphine (Fasano, Antonini, et al., 2020). The rotigotine patch would also be a reasonable alternative under these circumstances, although it is considered a less potent anti–parkinsonian drug compared to levodopa or apomorphine (Raeder et al., 2021). It could either replace or even complement the basic antiparkinsonian treatment, in cases when escalation is required. Intravenous administration of amantadine is another option, although it is considered less efficacious than levodopa and with more adverse events, and it is not available in all countries (Fasano, Antonini, et al., 2020).

5.2.1 General anesthesia

In severe cases where intubation and mechanical ventilation might be deemed necessary, general anesthesia medication might also cause, mostly minor, issues in PwP infected with SARS-CoV-2. There are no overall guidelines considering the care of PwP admitted in ICU and most information concerning the effect of general anesthetics and analgesics on PwP is based on case reports of PwP going through an operation. More specifically,

the concomitant use of MAO inhibitors and pethidine is contraindicated due to inhibition of serotonin reuptake and risk of serotonin syndrome (Zornberg, Bodkin, & Cohen, 1991). Halothane renders the heart more vulnerable to the action of catecholamines and may predispose to arrhythmias in patients treated with levodopa. Isoflurane, sevoflurane and enflurane have been reported as safer alternatives (Roberts & Lewis, 2018). Although propofol has been typically considered a safe agent to induce and maintain general anesthesia in PwP, bearing a favorable pharmacokinetic profile, it has been associated with a risk of triggering of dyskinetic and dystonic movements. Such phenomena, although unusual, have been effectively managed in published cases with the use of dexmedetomidine (Roberts & Lewis, 2018). Other anesthetics which have been associated with aggravation of extrapyramidal signs are fentanyl (Buxton, Gauthier, Kinshella, & Godwin, 2018; Zesiewicz et al., 2009), alfentanil and thiopental (Shaikh & Verma, 2011). Low doses of ketamine were reported to facilitate problematic airway management and tremor in PwP perioperatively (Wright, Goodnight, & McEvoy, 2009).

6. Other pharmacological interventions in Covid-19 and possible complications in PwP

Chloroquine and its derivative hydroxychloroquine with the combination of azithromycin used to be a first-line treatment in Covid-19 serious infections during the first months of the pandemic (Touret & de Lamballerie, 2020). However, their efficacy was not confirmed in randomized control trials, while their potential cardiotoxic effect (QT prolongation) renders their clinical use problematic (Ho et al., 2021).

A recent meta-analysis of non-randomized cohort studies has shown that anakinra, a recombinant IL-1 receptor antagonist might be related to reduced mortality and a lower risk of mechanical ventilation when administered in patients with severe Covid-19 (Pasin et al., 2021). It has a safe administration profile with no special contraindications for PwP or reported interactions with anti-parkinsonian medication (Anakinra. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet], 2012).

Ruxolitinib and tofacitinib are selective JAK inhibitors with promising results against severe Covid-19 according to ongoing research (Cascella et al., 2021). No absolute contraindications have been reported for administration in PwP or serious interactions with drugs commonly used in PD,

with the exception of clozapine due to the risk of QT prolongation, along with a potential additive hematological toxicity (neutropenia) (Dhillon, 2017; Gatti, De Ponti, & Pea, 2021). Both drugs are largely metabolized by the isoenzyme of CYP3A4, therefore treating physicians should be cautious with the co-administration of drugs which are strong inducers or inhibitors of this isoenzyme, like carbamazepine or valproic acid (Dhillon, 2017; Gatti et al., 2021).

It is generally advised vitamin D levels to be assessed in PwP, as vitamin D deficiency has been reported to contribute to PD clinical course (Fullard & Duda, 2020). In a large case-controlled survey in Italy, it was found that PwP non-supplemented with vitamin D were at greater risk of being diagnosed with Covid-19 compared to those who were well-supplemented, highlighting a potentially protective role of vitamin D (Fasano et al., 2020). In addition, administration of a moderate and well-calculated vitamin D3 dosage in PwP might help mitigate the effect of Covid-19 complications (Azzam, Ghozy, & Azab, 2022).

7. Usual complications in hospitalized PwP and Covid-19

7.1 Nausea

Nausea or vomiting are quite common among the constellation of Covid-19 symptoms (Andrews, Cai, Rudd, & Sanger, 2021). Metoclopramide, a dopamine D2 receptor antagonist, is an antiemetic typically used in the clinical setting to alleviate nausea in Covid-19 patients (Ai et al., 2020). However, it is generally advised for this drug to be avoided in PwP, due to its central mode of action and the potential of aggravating parkinsonism (Travagli, Browning, & Camilleri, 2020). The same applies for the dopamine antagonists in the category of phenothiazines, thioxanthenes and butyrophenones (Roberts & Lewis, 2018). Under these circumstances, the use of domperidone is preferred as, despite being a D2 receptor antagonist, it cannot cross the blood-brain barrier and exhibits a better tolerability and safety profile (Travagli et al., 2020). It should be noted, though, that domperidone can prolong the QT interval, increasing the risk of life-threatening arrhythmias; a QT interval exceeding 450 ms in men or 470 ms in women on the baseline ECG should prevent treating physicians from applying this therapy (Reddymasu, Soykan, & McCallum, 2007). However, a randomized controlled study conducted in healthy volunteers showed that this effect was absent in domperidone doses of less than

80 mg daily (Biewenga et al., 2015). Ondansetron, a selective serotonin 5-HT$_3$ receptor antagonist, might be a safe alternative for PwP with nausea or vomiting, although constipation could be an expected side effect (Wilde & Markham, 1996). Finally, the antihistamine cyclizine might be of use in PwP, with sedation, dizziness, confusion, palpitations, constipation, and urinary retention being the most common complications (Cyclizine, 2012; Roberts & Lewis, 2018).

7.1.1 Delirium

Delirium appears in one third of older general medical patients, with half of these cases occurring on admission and the rest during hospitalization, and can be a life-threatening emergency (Marcantonio, 2017). For patients under mechanical ventilation admitted in the ICU the percentage of delirium exceeds 75% (Ely et al., 2004). Older age, decreased functional status, cognitive impairment (even mild), depression and comorbidities constitute the most common predisposing factors for delirium, while a sub-jacent infection, acute or severe illness, pain, anemia, anesthesia and drugs (including sedative hypnotics and anticholinergics) are the most frequently encountered precipitating factors (Kalimisetty, Askar, Fay, & Khan, 2017; Marcantonio, 2017; Wakefield, 2002). Undernourishment and dehydration on admission might be aggravating factors (Wakefield, 2002). Delirium constitutes a common complication of Covid-19, especially in critically ill patients, and is associated with a poor outcome (Ticinesi et al., 2020). Lack of family visitation due to isolation regulations has also been identified as a potential risk factor (Pun et al., 2021).

Evidence suggests that PwP are more vulnerable to delirium when admitted to hospital and treating physicians should be vigilant to acknowl-edge early sings of agitation, confusion, or cognitive deterioration (Vardy, Teodorczuk, & Yarnall, 2015). In case of delirium, a number of non-pharmacological approaches could be applied. Treating physicians should check for newly introduced drugs, which might act as causative factors (such as opiates, fluoroquinolones) and could be discontinued or administered at a lower dose (Marcantonio, 2017). Electrolyte imbalances, infections, intra-cranial disorders (such as hemorrhages, tumors, CNS infections), urinary retention, fecal impaction and potential myocardial or pulmonary condi-tions (such as hypotension, hypoxia, anemia) should be properly addressed (Marcantonio, 2017). Use of eyeglasses and hearing aids, if applicable, should be encouraged to prevent decreased sensory stimulation, along with regular contact with family members, even remotely using virtual means. Patients

should be mobilized during hospitalization, even with assistance, and should be monitored for pressure ulcers (Marcantonio, 2017). It is better if the use of physical restraints is withhold, as it has been associated with a more prolonged state of delirium (Inouye et al., 2007). A non-pharmacological sleep-hygiene schedule, avoiding unnecessary patients' awakenings (such as nurse rounds for evaluating vital signs) and noise, preventing sleeping during the day and providing a hospital environment with adequate lighting during the day, along with a sufficient dietary intake (with proper supplementation if necessary) would also be helpful (Marcantonio, 2017). It is also important for staff to remember to reorient patients to time, place and person at least three times per day (Marcantonio, 2017). In case of hyperactive delirium, a serial tapering of anti-parkinsonian drug categories should be considered, starting with anticholinergics and then followed by MAO inhibitors, amantadine, dopamine agonists and COMT inhibitors (Ebersbach et al., 2019), although the order of dose reduction or discontinuation can be individualized. An abrupt cessation is not recommended. Sedatives, like benzodiazepines, should better be avoided, while low doses of antipsychotics can be used, if needed. For PwP, quetiapine and clozapine are considered as the safest options to avoid motor impairment, although no randomized studies have provided clear evidence on their use (Vardy et al., 2015). Quetiapine can be initiated at 25 mg and gradually increased to 100–150 mg daily, while clozapine can be started at 6.25–12.5 mg and gradually increased to 75–100 mg daily with regular monitoring for agranulocytosis (Ebersbach et al., 2019). The successful use of the cholinesterase inhibitor rivastigmine has also been described in a case report of a PwP developing delirium, but evidence considering its use is rather rare (Dautzenberg, Wouters, Oudejans, & Samson, 2003). Administration of prophylactic medication to prevent development of delirium is not recommended (Zoremba & Coburn, 2019).

7.1.2 Psychosis

Psychosis is a common complication in PwP, usually appearing later in the disease course (Schapira et al., 2017). Although dopaminergic therapy per se can induce psychosis, subjacent systemic conditions, including infections and Covid-19 in particular, or other drugs use, like antidepressants or painkillers, could also act as precipitating factors (Parra et al., 2020; Simonet et al., 2020). Psychotic symptoms in PwP typically manifest gradually, allowing for step-by-step approaches to minimize polypharmacy (Simonet et al., 2020). Underlying metabolic causes should be excluded or properly

addressed, if present. Similarly to delirium, a common strategy, which can be personalized, is to gradually taper anti–parkinsonian medication, starting from anticholinergic drugs and followed by MAO inhibitors or amantadine, dopamine agonists and COMT inhibitors (Simonet et al., 2020). An abrupt cessation is not recommended. Tricyclic antidepressants and opiates are also advised to be slowly withdrawn (Simonet et al., 2020). In case drug reduction is not feasible or psychosis persists despite the modifications, introduction of an atypical antipsychotic drug could be considered. Clozapine has been characterized as an "efficacious" and "clinically useful" option to treat PD psychosis, although specialized monitoring is required (Seppi et al., 2019). Although quetiapine has been characterized only as "possibly useful", it is more easily accessible in clinical practice due to its better tolerated profile (Seppi et al., 2019). Finally, pimavanserin has been recently labeled as "efficacious" and "clinically useful" in PD psychosis management with an acceptable safety profile (Seppi et al., 2019). The use of olanzapine, risperidone or other atypical antipsychotics is generally discouraged in PD psychosis due to exacerbation of parkinsonism, while evidence considering cholinesterase inhibitors (rivastigmine, donepezil) is conflicting and seem to be more efficacious in chronic rather than acute psychosis in PD (Goldman, Vaughan, & Goetz, 2011).

It is of interest that clozapine therapy, especially duration of therapy and not dosage, has been associated with an increased risk of Covid–19 infection (Aubignat, 2021). Following this observation, international recommendations have been drafted, stating that patients on clozapine with any Covid–19 symptoms should undergo a medical assessment and complete blood cell count (Siskind et al., 2020). In case they are diagnosed with Covid–19, the treating physician should consider reducing the dose of clozapine by half. The initial dose can be gradually resumed, starting 3 days after fever resolution (Siskind et al., 2020). No instructions have been given considering initiation of clozapine during a SARS-CoV-2 infection and all data currently available refer to patients with psychosis and not PD (Aubignat, 2021).

7.1.3 Orthostasis
Orthostatic hypotension appears in up to 58% of PwP (Schapira et al., 2017). In the setting of Covid–19, external factors like dehydration secondary to fever, diarrhea, reduced water intake due to anorexia, anemia or subjacent causes of cardiac dysfunction, including arrhythmias, should be excluded or

properly addressed (Simonet et al., 2020). The patient's regimen should also be reviewed with special concern on the use of antihypertensives or α-blockers, while almost all dopaminergic medication can precipitate orthostatic hypotension. In severe orthostasis attributed to dysautonomia in the context of PD, administration of fludrocortisone (0.1 mg once to three times daily), midodrine (2.5–10 mg three times daily) or droxidopa (300 mg three times daily) could be possibly useful (Seppi et al., 2019; Simonet et al., 2020).

7.1.4 Dysphagia—Nutritional intake difficulties

Malnutrition has been linked to impairment of the immune system, thus rendering individuals more susceptible to potential infections (Bourke, Berkley, & Prendergast, 2016). Immobilization and assisted breathing for extended time periods, which are common among hospitalized patients, especially those with impaired motor performance, lead to loss of muscle mass, resulting in an even more problematic recovery (Fernández-Quintela et al., 2020). Indeed, up to 60% of acutely ill were reported to be malnourished (Felder et al., 2015). Malnutrition in the context of Covid-19 might be a result of gastrointestinal complications, hypo-albuminemia, hypermetabolism and excessive nitrogen loss (Fernández-Quintela et al., 2020). In addition to the above, up to 80% of PwP might be suffering from dysphagia at some point of their disease course, which might predispose to aspiration (Suttrup & Warnecke, 2016). It is, thus, of the utmost importance for PwP inflicted with SARS-CoV-2 to achieve a sufficient caloric intake along with proper supplementation.

For PwP with dysphagia, a soft diet of adequate caloric content, high in fibers, is recommended with the addition of a liquid thickener if necessary (Arrigo et al., 2020). Instructing some patients to swallow following the chin-down posture might also be useful (Arrigo et al., 2020). In the Covid-19 era, having a speech or swallowing therapist to visit hospitalized patients might not be allowed, however, a video-assisted swallowing therapy might be possible via telemedicine services. Especially for those patients presenting with drooling and dysphagia, which is frequently encountered in advanced stages of PD, increasing the risk of aspiration, botulinum injections in the salivary glands might be indicated (van Wamelen et al., 2020). In severe dysphagia, treating physicians should consider inserting a nasogastric tube, not only to ensure sufficient caloric intake, but also to resume levodopa administration. Levodopa/Carbidopa

Intestinal Gel (LCIG) continuous infusion could be useful under these circumstances, as the percutaneous endoscopic gastrostomy (PEG) tube allows administration of nutrition and fluids. If this is not feasible, subjacent apomorphine, transdermal rotigotine or intravenous amantadine could be reasonable options to avoid an abrupt cessation of dopamine replacement therapy.

8. Conclusion

The Covid-19 pandemic has disrupted healthcare services and patients' routine and quality of life worldwide. This is of particular importance for PwP, as they are required to balance between minimizing the risk of contracting SARS-CoV-2, while getting access to the best possible care for their PD symptoms and maintaining a healthy way of living (exercise, physiotherapy, social interactions). Providers should be aware of potential delays in care delivery, especially in relation to advanced therapies. Under these circumstances, this health crisis provides an opportunity for healthcare professionals to develop and incorporate standardized tools and services for diagnosis and management for chronic conditions, like PD, remotely, using virtual means with respect to local regulations.

The recurrent infection outbreaks have increased frustration and placed an overwhelming burden to hospitals around the globe, with the recent omicron SARS-CoV-2 variant spreading rapidly. Despite the expected high transmissibility of this new variant and the numerous reported re-infections, no alarming clinical concerns have arisen up to now, thus, therapeutic protocols have not been modified yet, although there is a possibility that monoclonal antibodies efficiency might be compromised (Karim & Karim, 2021). PwP are strongly advised to get vaccinated, as the combination of public health prevention measures and vaccination has been associated with a much lower risk of severe disease, hospitalization and death, especially among the elderly (Karim & Karim, 2021). Treating physicians should remain vigilant to acknowledge early signs of complications related either to PD or Covid-19, appropriately guide their patients and timely introduce any interventions. Especially during hospitalization of PwP affected with SARS-CoV-2, the role of a consulting neurologist with special knowledge on movement disorders is crucial and might affect the patients' outcome.

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