Review

Management of Advanced Therapies in Parkinson's Disease Patients in times of Humanitarian crisis: the COVID-19 experience

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Abstract

Background. While the COVID-19 pandemic is affecting a relatively small proportion of the global population, its effects have already reached everyone. Global attention has been largely focused on infected patients and the frontline responders. However, the pandemic has the potential to differentially disadvantage the physical and mental health of many chronically ill patients, including those with Parkinson's disease (PD).The first healthcare reaction has been to limit access to clinics and neurology wards and in some regions shortage of medical staff has forced movement disorders neurologists to provide care for COVID-19 patients. In an attempt to preserve fragile PD patients from being infected, appointments have been postponed and many have been left without appropriate alternatives to obtain a consultation.

Objective. To share the experience of various movement disorder neurologists operating in different world regions and provide a common approach to patients with PD, with a focus on those already on advanced therapies, which may serve as guidance in the current pandemic and for emergency situations which we may face in the future.

Conclusion. Most of us were unprepared to deal with this condition, given that in many health care systems telemedicine has been only marginally available or only limited to email or telephone contacts. In addition, to ensure sufficient access to intensive care unit beds, most elective procedures (including deep brain stimulation or initiation of infusion therapies) have been postponed as they are classified as "non-urgent".
We all hope there will soon be a time when we will return to more regular hospital schedules. However, we should consider this crisis as an opportunity to change our approach and encourage our hospitals and health care systems to facilitate remote management of chronic neurological patients including those with advanced PD.

Introduction

Over the past 20 years, pandemics such as severe acute respiratory syndrome coronavirus (SARS Co-V),[1] Middle Eastern respiratory syndrome (MERS),[2] and influenza (H1N1 and H5N1) have placed a strain on the healthcare systems and societies. It's now the turn of SARS Co-V2, which emerged in the region of Wuhan in China around December last year and spread so rapidly that the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020. The virus shares highly homologous sequences with SARS Co-V and although most subjects may be asymptomatic or only develop mild upper respiratory symptoms, more severe manifestations occur, including acute respiratory distress syndrome (ARDS) eventually resulting in coma and death.[3]
Severe neurologic complications have been associated to human coronavirus infections but to date, no rigorous evidence exists of direct neurologic involvement of the novel SARS Co-V2 (Table 1).[4] Most of these manifestations are unspecific and generally associated to viral infections, such as dizziness, headache and myalgia. Anosmia and ageusia have been consistently described but their pathophysiology is still unclear.

In this view-point-review we want to share the experience and opinion of various movement disorder centers operating in different world regions in order to discuss the impact of the current humanitarian crisis of COVID-19 on Parkinson disease (PD) patients on advanced therapy and provide a common approach to their care. We decided to focus on PD patients already on advanced therapies as they inherently feature a baseline frailty greater than PD on oral medications. In addition, due to the complexity of their treatment (i.e. device-aided and requiring parameter adjustments), they pose a greater challenge to the medical system. In fact, with restrictions on travel being imposed and all elective patient appointments being cancelled, there is an urgent need for alternative models of care (e.g. teleneurology).

COVID-19 and Parkinson's disease

The COVID-19 pandemic has forced health systems to rapidly change priorities in medical care and this has had a dramatic impact on many patients with chronic conditions including those with PD. Hypertension, diabetes, obesity seem to stand out as the most common comorbidities in patients with more severe manifestations of the infection. In addition, men, the elderly and immunocompromised persons are particularly vulnerable. Many have underlying neurological comorbidities, thus raising three questions: 1. Does advanced PD pose an increased risk of morbidity and mortality in COVID-19 patients? 2. Does SARS Co-V2 complicate the clinical course of PD? 3. How we can manage PD patients on advanced therapies in times of this pandemic and during future humanitarian crises will be the focus of the sections below.

Does advanced PD pose an increased risk of morbidity and mortality in COVID-19 patients?

Physical frailty in older adults is common and associated with a wide range of adverse health outcomes including mortality and higher disability.[5]. Frailty may occur in up to 50% or more of adults by the age of 85.[6] Accurately identifying frailty in patients with PD may have prognostic and therapeutic implications, since the diagnosis of frailty carries significance for quality of life, morbidity and life expectancy.[7-10]
Frailty has been shown to be common in PD, affecting 22.2% of community-based patients.[11] PD patients are nearly twice as likely to be admitted to hospital for complications of the disease and its treatment than for management of the primary motor deficit, with pneumonia being the second commonest diagnosis in most of the studies.[12]

Little information is available on the relationship between PD and humanitarian crises. Of 631 UK patients hospitalized during the first pandemic wave of H1N1, neurological comorbidities failed to correlate with disease severity or duration of hospitalization, with a likelihood ratio of 1.21 (0.34–4.25, p=.764).[13] A retrospective study of 397,453 patients aged ≥60 years with Parkinsonism found lower in-hospital mortality than those patients without Parkinsonism (odds ratio= 0.81; 95% confidence interval= 0.74–0.89). However, length of stay was 8.1% longer in patients with Parkinsonism, who were also less likely to be discharged home (0.62; 0.58–0.67). Higher age, lower body mass index, lower Barthel index, higher A-DROP (Age, Dehydration, Respiratory Failure, Orientation Disturbance, and Blood Pressure) score, and a Charlson comorbidity index ≥3 were significantly associated with higher in-hospital mortality. The study suggests that in-hospital mortality due to pneumonia is not higher in parkinsonian patients, but it is not clear that this applies to those who have developed advanced ARDS.[14] In another retrospective study, mortality was 12.5% after the ICU admission in 62 PD patients with sepsis and variable age, duration and severity of underlying conditions. In addition, a Hoehn and Yahr score >3 were associated with higher mortality, which also increased over the 18 months of follow-up and only 38% of these patients returned home.[15]

Another source of information comes from studies exploring the effect of earthquake or war on PD patients, most of which described a worsening of symptoms due to the combination of stress on motor and mental function as well as limited healthcare resources (e.g. lack of doctors and anti-PD medications).[16, 17] Interestingly, some of these patients presented an unexpected improvement of their motor function attributed to paradoxical kinesia and lasting up to 4 months.[18] Given its variable occurrence, it has been argued that cognitive impairment is needed for such paradoxical improvements.[19]

Presently, there is insufficient evidence in the literature showing that PD by itself worsens COVID-19 outcome.[20] However, patients with advanced PD with restricted pulmonary capacity due to axial akinesia are at higher risk for pulmonary decompensation. In addition, it is well known that Parkinsonism tends to decompensate with acute stress and particularly with fever, both key symptoms of COVID-19.[21] During these circumstances, PD patients are at risk of developing severe generalized akinesia or akinetic crises, and levodopa dose may require a rapid increase.[22]

Does SARS Co-V2 complicate the clinical course of PD?

SARS Co-V1 has been detected in the CSF of a patient with encephalitis and acute respiratory distress syndrome.[23] SARS Co-V2 has been recently reported to cause meningoencephalitis in a 24-year-old man and encephalopathy in a 74-year-old PD patient.[24, 25] Does COVID-19-associated anosmia suggest the involvement of the olfactory bulbs? In mouse models of coronavirus encephalitis, the virus can enter the brain trans-neuronally through the olfactory pathways. Indeed, it has been argued that SARS Co-V2 might have a direct detrimental effect on bulbar respiratory centre.[26] Interestingly seropositivity for coronaviruses has been reported in a variety of neurological disorders also including PD.[27] The significance of these findings is not clear but there are authors also hypothesizing an increase of PD incidence in COVID-19 survivors,[21] although in many case anosmia is transient, suggesting it does not affect olfactory neurons.

Theoretical uncertainties aside, PD patients are certainly facing increased levels of stress that may have several short-term as well as long-term adverse consequences (Figure 1). In fact, dopamine-dependent adaptation is a requirement for successful coping that, when deficient, leads to a sense of loss of control and increased psychological stress, thus explaining the well-known motor worsening that PD patients experience under stressful circumstances. In addition, stress probably hampers the many compensating

mechanisms in a Parkinsonian brain. Finally, stress as well as motor problems further engage in a vicious circle with additional nonmotor problems such as insomnia or constipation.[21]

The stress on healthcare systems

The first reaction of the medical community has been to limit the access of non-urgent patients to clinics and wards. In some regions shortage of medical staff has forced movement disorders neurologists to provide care for COVID-19 patients. In an attempt to prevent fragile PD patients from being infected, appointments have been postponed and many have been left without appropriate alternatives to obtain a consultation. Most neurologists were unprepared to deal with this condition as in many health care systems telemedicine has been only marginally available or only limited to email or telephone contacts. In addition, to ensure sufficient access to Intensive Care Unit (ICU) beds, most elective surgical procedures have been delayed including deep brain stimulation (DBS). The initiation of infusion therapies such as levodopa-intestinal gel (LCIG) or apomorphine have also been postponed as they are classified as "non-urgent". Furthermore, many patients have deliberately chosen to skip appointments due to the fear of being exposed to the risk of the contagion.[28]

Management of Advanced Therapies

Regardless of the device-aided treatment in place, the first step is an accurate triaging of patients in the current scenario. Figure 2 depicts the general approach to this process. At Toronto Western Hospital 25% of the visits have been postponed, 75% converted into a telemedicine visit and 5% kept as originally planned as in-hospital visits. Reassurance should be given to patients that emergency care will remain accessible if absolutely necessary and the health care provider should make sure the patients or carers (or nursing home staff, if applicable) have all the necessary phone numbers. In addition, the manufacturer´s product specialists are available to be contacted by phone or – in selected cases and depending on the geography – they can also provide home visits on a regular basis or when needed (using appropriate personal protective equipment), although this may be difficult during lockdown. Manufacturers can also ship pieces of equipment, e.g. to replace malfunctioning pumps or patient controllers. It is recommended that the patient has emergency numbers, both to the healthcare centre (PD nurse or doctor) and the company providing these devices.

The following sections will discuss in more details the approach depending on the type of advanced therapy.

Levodopa/Carbidopa Intestinal Gel Continuous Infusion

The treatment with LCIG was developed in the 1990's and was launched in 2004.[29] More than 12000 PD patients are treated worldwide with LCIG. A similar intestinal gel containing levodopa, carbidopa plus entacapone was recently launched in the Scandinavian countries, Levodopa Entacapone Carbidopa Intestinal Gel (LECIG).[30] LCIG/LECIG is a cellulose gel containing 20 mg/mL of levodopa. The gel is delivered continuously by a portable pump via a catheter through a percutaneous endoscopic gastrostomy (PEG) to the upper part of the small intestine. LCIG/LECIG is mostly given as a monotherapy but can be combined with other peroral/transdermal drugs. The treatment is normally given as daytime (16-hour) treatment but can, if needed, be given as 24-hour treatment.[31] Common effects when switching from oral standard therapy in patients with fluctuating PD include a 65% reduction of time in "off", and improvements of dyskinesias, non-motor symptoms, activities of daily living (ADL) function and health-related quality of life. At initiation, the dose is titrated either by initial nasoduodenal catheter or directly after a permanent catheter is placed in the jejunum through the PEG-J with a gastroscopic technique. Adverse events most commonly relate to the PEG surgery and/or the infusion device and

include infections, peritonitis too. The majority of adverse events occur during the first weeks after the PEG implantation.[29]

Is the use of LCIG increasing patient's risks during a pandemic/other crises?
Patients with PD are often elderly and may be more prone to pneumonia and other infections but there is no case report or even theoretical reason to believe that LCIG/LECIG therapy would increase the patients' risks during an infection or other crisis. To the contrary since LCIG/LECIG treatment improves motor status, ADL function and many non-motor aspects, it could theoretically improve the patients' capacity to deal with an infection or other crisis by diminishing off-period duration. Nevertheless, initiations of new patients on LCIG should be postponed during a public health crisis such as a pandemic.

Care of systemic issues (infections, organ failures) in LCIG patients
There are no indications that LCIG/LECIG treatment would be a disadvantage compared with oral treatment when patients have other severe illnesses, e.g. a severe infection and/or organ failure. Since LCIG/LECIG gives a reliable and stable non-oral delivery of dopaminergic drug, resulting in a more stable motor control, LCIG/LECIG may instead be an advantage compared to oral/transdermal treatment.

Care of LCIG patients in times of humanitarian crisis
It is convenient for healthcare centres to establish routines for video consultation (see below). Apart from the consultation, it can also be valuable to get objective and quantitative monitoring of the patients' status,[32, 33] for example also monitoring the status of the PEG (Figure 3A). The programming of the pump and thereby the dosing of LCIG/LECIG can mostly be handled by the patient/caregiver after instructions from the doctor/nurse over telephone/video. The pump can be kept in a non-locked mode to make this process easier, although this should be weighed against certain risks, as in patients with a history of dopa dysregulation syndrome.
A delivery service for the transport of LCIG/LECIG from the pharmacy to the patient is beneficial. However, in case of LCIG/LECIG delivery difficulties, the patients should have instructions for emergency medication use – normally a scheme for oral levodopa therapy and storage of the corresponding oral medication (Table 2).

Strategy in case of sudden failure/withdrawal of the therapy
In case of pump failure, most countries have an emergency telephone number, where the patient/caregiver can get advice on how to solve the problem or get a quick delivery of a new pump. In the meantime, the patient shall use his/her peroral emergency medication (Table 2).
In case there is a blockage in the catheter, the patient/caregiver should have a checklist with steps that they can take themselves. If this does not help, contact with the hospital is necessary and the patient has to take immediately switch to his/her peroral emergency medication prescription. If there is a suspicion that the catheter has been displaced to the stomach (resulting in an irregular effect of the medication), the patient can continue the pump treatment and repositioning of the catheter to the jejunum should be performed when possible.

Subcutaneous Apomorphine Continuous Infusion
Apomorphine is a highly efficacious dopamine agonist administered subcutaneously, either as intermittent injections for fast relief from OFF symptoms, or as a continuous infusion using various externally worn mini-pump systems. Apomorphine continuous infusion has been shown to lead to significant and marked OFF time reduction and increase in ON time without troublesome dyskinesia.[34]
Apomorphine typically replaces some or even all of a patient´s oral medication during the daytime and

24-hour use is possible. Adverse effects include skin changes, nausea, somnolence, neuropsychiatric issues, orthostatic hypotension, ankle edema and, rarely, drug-induced immune hemolytic anemia.[35] The frequency and type of routine follow-up and clinic visits varies among health care systems.[36, 37] Routine blood checks are typically done every 3-12 months, however no interval can be defined that would guarantee early detection of haemolytic anemia. Therefore, centres typically provide information to the patients and carers on the symptoms of possible anemia.

Is the use of apomorphine increasing patient's risks during a pandemic/other crises?
The full clinical spectrum of COVID-19 is not yet known but to date, there is no suggestion of features that would directly interfere with the use of apomorphine. Initiations of new patients on apomorphine should be postponed during a public health crisis such as a pandemic. However, among the device-aided therapies apomorphine infusion remains the easiest to implement.

Care of systemic issues (infections, organ failures) in apomorphine patients
If PD patients using an apomorphine infusion require in-patient or ICU admission because of COVID, continued use of the infusion system may be difficult because specific training is required to manage the pump system. If this is not feasible, apomorphine can be switched to a regular infusion system which delivers the usual hourly flow rate into the subcutaneous tissue, usually during daytime only. In patients who have used 24 hour apomorphine before entering the ICU, this should be maintained if possible (see below). If apomorphine vials are not available or the acuity of the situation does not allow setting up an extra infusion system, oral levodopa should be used (Table 2).

Care of apomorphine pump patients in times of humanitarian crisis
Routine laboratory tests should be postponed. Sending pictures of skin changes may be sufficient and may avoid personal visits. During prolonged crises and under certain circumstances, it may be possible to guide a patient or carer through the steps of unlocking the pump and changing the flow rate, although persons with impaired manual dexterity, cognitive issues or lack of experience with technical devices in general will find this difficult. The clinicians should make the judgement whether this can be done safely, particularly when the alternative would be to discontinue the infusion, which would also pose risks that would be difficult the manage remotely. Pre-set various flow rates for different times of the day, or for daytime and nighttime, is also a useful tool to consider. However, during a public health crisis any changes should only be made if deemed necessary because of the reduced capacity to respond to the potentially resulting deterioration in the patients´ state.

Strategy in case of sudden failure/withdrawal of the therapy
As with levodopa, sudden withdrawal of apomorphine infusion typically leads to marked motor worsening including malignant akinesia, particularly if it has provided a large proportion or all of a patient´s dopaminergic treatment. Dopamine agonist withdrawal syndrome, including acute lethargy, may also occur.[38] Therefore, centres that initiate patients on apomorphine infusion should provide recommendations on how to proceed in case of pump failure or withdrawal of apomorphine for any reason, e.g. as part of their initial discharge summary letters. The typical recommendation is the return to the patient´s oral medication prior to pump use, plus additional oral levodopa as required until the issue can be fixed. However, this may no longer be the best choice in patients who have used apomorphine for many years and where the illness itself has progressed. In these patients, levodopa monotherapy may be more appropriate (Table 2). Patients or carers should be reminded that a larger than usual supply of oral replacement medication should be obtained and kept at home.

Deep Brain Stimulation

DBS is a common treatment option for patients with PD, with good effects on motor complications such as fluctuations and dyskinesias, resulting in an improvement of quality of life.[39] On-label DBS targets are the subthalamic nucleus (STN), the globus pallidus pars interna (GPi) or the ventral intermediate (Vim) nucleus of the thalamus. STN and GPi stimulation can improve motor complications and cardinal signs of the disease while Vim stimulation only improves tremor.[39] DBS systems comprise an implantable pulse generator (IPG), connecting wires and brain electrodes. People with implanted DBS systems have additional distinct specific needs as a result of this therapy. For example, IPGs can be rechargeable or function as 'primary cells': the former can last between 10 and 25 years whereas the latter require replacements every 3-5 years.[40] Disease progression or the development of chronic DBS provoked symptoms such as gait freezing or dysarthric speech require programming sessions, which are usually in-person visits.

Is the use of DBS increasing patient's risks during a pandemic/other crises?
There is no suggestion that a viral respiratory infection would directly interfere with the use of DBS. However the majority of clinicians confronted with a DBS patient will not be comfortable with the methods of programming of the DBS, checking its normal functioning nor will they be confident whether the DBS itself poses additional risks/challenges in the context of potentially changing healthcare needs, e.g. cardiac monitoring (see below). Commonly, changes in PD symptom severity may be attributed to the DBS by the unwary, while in reality often result from common problems such as infections, constipation or metabolic upset.

Care of systemic issues (infections, organ failures) in DBS patients
If PD patients on DBS therapy require in-patient or ICU admission, continued use of DBS is recommended because of the major worsening of motor function as well as onset of painful rigidity that can accompany prolonged withdrawal of DBS. In addition, DBS also provides PD treatment when dopaminergic drug delivery cannot be guaranteed. This is particularly relevant to STN DBS as it allows a greater medication reduction than GPi DBS.[39] A possible limitation introduced by DBS is the electric artifact on EEG or ECG traces.[41] This can be managed either by turning the DBS off for few minutes during the ECG/EEG acquisition (easily possible by using the patient's own controller) or – whenever not possible (e.g. severe tremor, prolonged monitoring) – by using a bipolar DBS configuration, i.e. both anode and cathode are on the lead, thus resulting in a narrow electrical field around the electrode (this requires input from the DBS specialist team).[40]

Care of DBS patients in times of humanitarian crisis
Familiarity with the common problems associated with DBS, allows experienced clinicians to spot when a new set of symptoms requires detailed investigation or those occasions when it may be more likely amenable to minor DBS adjustments. These types of issues can be readily detected through telephone or video consultation but nevertheless require clinicians that are confident and experienced in dealing with DBS. It is therefore vital that all DBS patients have access to specialist advice whenever necessary.

It is not uncommon for people with DBS to develop new symptoms or even new adverse effects of DBS despite previously optimized parameters. All the modern DBS platforms allow patients to adjust their DBS parameters within pre-arranged windows by means of controllers that can access the implanted hardware with telemetry. Patients should be always educated how to use their own patient controllers to allow fine tuning of settings as well as performing battery checks on a regular basis. In the absence of face to face consultations, video consultations can greatly facilitate checking and verifying that settings and battery life are as they should be, or to help remotely instruct patients how to make minor DBS adjustments (Figure 3B).

Options for alternative stimulation programs can also be pre-programmed into modern IPGs. Alternative stimulation settings may be made available in anticipation of future eventualities and permitted for patients with sufficient technical competence.[42] However, it is not usually possible to anticipate and pre-emptively make settings available in the long term with the range of possible changes in symptoms that may occur as a result of disease progression. Sudden failure of symptom control especially in the context of falls/head injury, or signs of local DBS infection typically need urgent face to face consultation to interrogate the normal functioning of the hardware and any further investigations/neurosurgical input. For some of these scenarios it is however possible to screen the condition with telemedicine (Figure 3C). The most common source of sudden withdrawal of the therapy is end of battery life, which must be avoided by ensuring that the battery level is appropriately checked by either the patient or a clinician on a regular basis.

Strategy in case of sudden failure/withdrawal of the therapy

It must be clearly communicated that sudden DBS failure can constitute a medical emergency caused by a life-threatening akinetic crisis similar to a neuroleptic malignant syndrome ('malignant STN DBS withdrawal syndrome').[43] Timely replacements should be continued even during times of crisis/emergency to prevent more substantial emergency care being subsequently required, although different scenarios and prioritization of patients should be kept in mind (Table 3). High doses of levodopa can be established in these cases but response might be poor after many years on lower doses.

A framework for better care

PD patients treated with advanced therapies typically show high symptom variability that requires frequent monitoring. Especially in the early phases of treatment with advanced therapies, it is critical to monitor treatment responses in order to optimize the titration and monitor for serious motor and nonmotor adverse effects (including autonomic instability and neuropsychiatric complications). With the COVID pandemic, PD experts have rapidly found themselves operating in an evidence-free zone where the virus' mitigation measures have created an urgent need to check in on advanced therapy PD patients' welfare.

Telemedicine or Virtual Distance Consultation

Telemedicine is the use of electronic information and communication technology to provide and support healthcare when distance separates participants. It is traditionally subdivided into synchronous (interactive video connection) and asynchronous telemedicine (store-and-forward transmission of medical images and/or data).[44] Telemedicine encompasses a broad range of health care tools, including body-worn sensors or smart homes equipped with sensors. The epidemic has already driven rapid innovation and implementation of these systems for the delivery of urgent and ongoing health care. A major benefit of expanding telehealth with no restrictions would reduce person-to-person contact between health service providers and COVID-19 and reduce the risk of exposure of noninfected but susceptible patients in waiting room areas. The Telemedicine Study Group of the International Parkinson and Movement Disorders Society has recently updated a guide to Telemedicine to reflect these recent changes.[45]

Telehealth can support both physical and psychosocial needs of patients with chronic disease irrespective of geographical location. Simple communication methods such as e-mail and text messaging should be used more extensively to provide general support,[46] especially as a suitable modality for lower-income regions or for areas lacking the bandwidth and continuous connectivity to perform synchronous telemedicine.[44] Another benefit of asynchronous telemedicine is that videos can be obtained for patients experiencing paroxysmal movement disorders.

Nevertheless, for many people with PD video-conferencing is widely accessible and can provide clinicians with useful motor and nonmotor assessments of patients symptoms,[47, 48] also approved of by patients.[49] Video assessments of parkinsonian symptoms or dyskinesias are helpful. In most cases, the advice given during telemedicine sessions will refer to simple strategies, such as changing the dosages of oral medications or the duration of pump use.
Important limitations of video conferencing are acknowledged, yet a modified version of the motor UPDRS without rigidity and retropulsion pull testing is reliable as well as guidelines for filming gait and movement disorders.[50, 51] The feasibility of conducting the Montreal Cognitive Assessment remotely in patients with movement disorders has also been proved.[52]

Ambulatory movement measurement devices can be mailed out to patients prior to telehealth appointments. Results can be readily available prior to the appointment and provide a longitudinal assessment in an ecologically valid setting. These data can improve communication between clinicians and patients and help identify and measure a range of motor and nonmotor problems remotely. They have been suggested to provide useful additional information to assess the DBS effect on motor symptoms in PD and can aid in the optimization of advanced therapies once instituted.[53] A portable monitoring system is also possible although the elements necessary for the remote assessment still require formal testing.[54]

Remote programming
The current pandemic highlights the urgent need for further innovation in particular around remote access to device programming. Hopefully, implementation of remote programming capabilities will progress before the results of pilot studies reported hitherto.[55-57] Telemedicine has been used in one small open-label study to assist with LCIG titration where it was found to be more resource-efficient, technically feasible, well-accepted and satisfactory to patients, neurologists, and nurses than hospital-based management.[56] Although pilot studies have been performed,[55] to our knowledge, no pump system is currently in clinical use that would allow for remote programming of apomorphine infusion settings.

Canada is home to one of the most established telemedicine programs: the Ontario Telemedicine Network (OTN), which is being operated through a secure Internet-based system since 2001. OTN provided telehealth services to 785,986 patients, over 1200 patients with movement disorders in 2017, and continues to provide care for advanced PD patients, including those with DBS.[57] Jitkritsadakul et al. analyzed the possibility of an 'indirect' intervention on DBS parameters, supervised by an expert physician through OTN and physically enacted directly by the patient or caregiver by means of the patient's controller.[57] The number of video-guided visits directly correlated to the distance between home and the DBS referral center, allowing a significant reduction in the logistical burden associated with travel time and costs. The volume of these visits has increased since the beginning of pandemic, also using less conventional systems such as Zoom or Skype (Figure 2B) (Table 4). This is the result of the lifted restrictions on sensitive data/privacy (e.g. HIPPAA) to contrast this unprecedented request of healthcare access, although there is a country-specific regulatory landscape.[58]

DBS stimulation parameters and infusion systems parameters could theoretically be modified directly from a remote location via a Bluetooth-based programming system installed at the patient's home. PINS Medical (Beijing, China) and SceneRay Corporation Ltd. (Suzhou, China) are two DBS manufacturers established in 2008 and 2015, respectively. They both promote web-based, remote, wireless DBS programming systems, in which patients may have their DBS settings adjusted at home by a clinician remotely located in a hospital or clinic.[59-61] These systems are only available in China and it's unclear if

they will ever reach the global market. Abbott systems, on the other hand, also features a locked capability for web-based remote programming, which is currently under investigation. A 6-month pilot study on 32 PD patients enrolled in a prospective, double-blind study, is currently undergoing in Australia. Patients are randomly assigned to remote care paradigm or standard of care protocol. For the first session, all subjects are connected to an experienced programmer remotely via a mobile platform while being in a clinic room with another expert programmer. A third blinded assessor determines programming effectiveness acutely (20 mins post session) and over time (3 weeks post first follow-up programming session). The primary endpoint is to evaluate the safety of the remote care paradigm. Secondary endpoint is the difference in UPDRS-III scores between first follow-up programming and 3-week assessment.[62]

Other roles of telemedicine

The validity of telemedicine to assess PD patients has been well documented in many studies, which is feasible because most physical examinations can be visualized (for a review see[63]). Other scopes are easily implementable and already tested. Telerehabilitation – also including speech therapy, a common problem in DBS and advanced cases – is possible as well as telepsychiatry, which was recently tested in a cohort including many DBS patients.[64] Education of healthcare providers in the community (e.g. general neurologists) and patients is also very valuable. Webinars and informative websites issued by hospitals and patient organizations around the globe are already heavily implemented.[21] These same platforms can be used for online singing, exercise or dancing classes for PD patients.

PD in the ICU

There are no guidelines detailing the care strategy for PD patients admitted in the ICU,[65] particularly with respect to the COVID-19 pandemic. As detailed before, efforts should be put in place to guarantee anti-PD therapy although the severity of clinical manifestations may require changes in therapeutic regimen. In case of pneumonia, physicians must ensure the maintenance of previous PD medications especially the adequate dosages of levodopa to avoid rigidity with contractures and respiratory impairment with reduced vital capacity and peak expiratory flow.[22]

In a severely akinetic patient with dysphagia, the easiest, cheapest and most efficient way of rapidly adapting PD therapy is by means of highly fractionated doses of levodopa solution infused with a nasogastric tube, typically administrated every 2-3 h intervals day and night. However, COVID-19 causes not only severe interstitial pneumonia but determines diffuse thrombosis secondary to direct viral diffuse endothelial damage.[66] Most subjects need to initiate anticoagulant therapy beside invasive mechanical ventilation which is in some cases continued for over one-two weeks. Therefore while in principle administration of levodopa through a nasogastric tube is advisable it may not be practical given the enormous pressure on physicians and nurses working on COVID-19 ICU.

Apomorphine pump therapy and LCIG could be continued if already implemented (see above). Using apomorphine when oral administration of any drugs is not possible has been recommended even in patients without prior exposure to apomorphine, e.g. perioperatively,[67] although in the setting of an acute COVID-19 ICU this approach can only be considered if malignant akinesia poses a real risk to the patient.

The only other broadly available non-oral antiparkinsonian drug is transdermal rotigotine but it is considerably less efficacious than levodopa or apomorphine and can be considered as a minimal bridging measure to avoid severe withdrawal symptoms. Similarly, intravenous amantadine is commercially available in some countries but it is less efficacious, although its theoretical property of blocking a pore in the envelope protein of SARS-CoV makes it an attractive – not yet tested – treatment.[68, 69]

Conclusions

In the recent past there have been many major epidemics. This includes Ebola, Zika, Dengue, Chikungunya, acute flaccid myelitis and H1N1 influenza, to name a few. Yet telehealth has received a push back in many healthcare systems, for the past 10 years in the USA for example, and in the EU due to data protection concerns. There are still many regulatory unknowns, such as medical license issues for patients seen from out of province/country or liability and billing uncertainties. In any case, an effective uptake of telemedicine strategies at this time will likely minimize the impact on physical and mental health in this vulnerable population of patients - both on a short- and long-term basis.
The COVID-19 pandemic is an opportunity to change our approach to chronic neurological patients, including those with advanced PD, particularly encouraging our hospitals to facilitate the use of tools for remote management and companies to develop an easy, validated and reliable remote access control of IPGs and continuous delivery pumps. The medical community should promote initiatives to evolve and standardize the kinematic measurement of motor function, including rigidity and gait. In conclusion, the COVID-19 pandemic is teaching us many lessons, such as the pivotal role of levodopa in case of system failure for any advanced therapy or the effect of social distancing and lockdown measures on frail patients with PD. In fact, this crisis also calls for the rapid introduction of better self-management strategies that can help patients to better deal with the challenges of social distancing and the other consequences of this crisis.

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Authors' Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

AF: 1A, 1B, 1C, 3A

AA: 1B, 1C, 3A

RK: 1B, 1C, 3A

PK: 1B, 1C, 3A

PO: 1B, 1C, 3A

AHE: 1C, 3A

TF: 1B, 1C, 3A

JV: 3B

MM: 1A, 1B, 3A

Full financial disclosure for the previous 12 months

AF

Stock Ownership in medically-related fields	None
Intellectual Property Rights	None
Consultancies	Abbvie, Abbott, Medtronic, Boston Scientific, Ipsen
Expert Testimony	None
Advisory Boards	Abbvie, Abbott, Boston Scientific, Ipsen
Employment	None
Partnerships	None
Contracts	None
Honoraria	Abbvie, Abbott, Medtronic, Boston Scientific, UCB, Ipsen
Royalties	None
Grants	Abbvie, Medtronic, Boston Scientific
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AA

Stock Ownership in medically-related fields	
Intellectual Property Rights	
Consultancies	
Expert Testimony	
Advisory Boards	
Employment	
Partnerships	
Contracts	
Honoraria	
Royalties	
Grants	
Other	

RK

Stock Ownership in medically-related fields	None
Intellectual Property Rights	None
Consultancies	None
Expert Testimony	Zambon
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Employment	None
Partnerships	None
Contracts	None
Honoraria	AbbVie, AOP Orphan, Bial, Britannia, Ever Pharma, Gruenenthal, Stada, UCB, Zambon
Royalties	None
Grants	Biotie, Britannia, Stada, Zambon
Other	None

PK

Stock Ownership in medically-related fields	None
Intellectual Property Rights	None
Consultancies	none
Expert Testimony	none
Advisory Boards	None
Employment	None
Partnerships	None
Contracts	None
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Other	None

PO

Stock Ownership in medically-related fields	None
Intellectual Property Rights	None
Consultancies	Abbvie, Britannia, Lobsor, Nordic Infucare, Stada
Expert Testimony	Lobsor
Advisory Boards	Abbvie, Britannia, Lobsor
Employment	None
Partnerships	None
Contracts	None
Honoraria	Abbvie, Britannia, Lobsor, Nordic Infucare, Stada
Royalties	None
Grants	Abbvie
Other	None

AHE

Stock Ownership in medically-related fields	
Intellectual Property Rights	

Consultancies	
Expert Testimony	
Advisory Boards	
Employment	
Partnerships	
Contracts	
Honoraria	
Royalties	
Grants	
Other	

TF

Stock Ownership in medically-related fields	None
Intellectual Property Rights	None
Consultancies	Boston Scientific, Bial
Expert Testimony	None
Advisory Boards	Voyager Therapeutics
Employment	None
Partnerships	None
Contracts	None
Honoraria	Boston Scientific, Profile Pharma
Royalties	None
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Other	None

JV

Stock Ownership in medically-related fields	None
Intellectual Property Rights	None
Consultancies	None
Expert Testimony	None
Advisory Boards	Boston Scientific, Medtronic, Newronika
Employment	None
Partnerships	None
Contracts	None
Honoraria	Boston Scientific, Medtronic, Zambon, UCB, Bial
Royalties	None
Grants	German ministry of research and education, Boston Scientific and Medtronic
Other	None

MM

Stock Ownership in medically-related fields	None
Intellectual Property Rights	None
Consultancies	None
Expert Testimony	None
Advisory Boards	None
Employment	None
Partnerships	None
Contracts	None
Honoraria	None
Royalties	None
Grants	None
Other	None

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Table 1. Neurologic complications have been associated to human coronavirus infections (modified from[24, 70, 71])

Condition	**Associated to SARS Co-V2**	**Associated to other human coronavirus**
Acute necrotizing encephalitis*	Yes	No
ADEM	No	Yes
Coma/encephalopathy*	Yes	Yes
Critical illness neuromyopathy	Yes	Yes
Encephalitis/meningitis	Yes	Yes
GBS/neuropathy	Unclear	Yes
Headache*	Yes	Yes
Myalgia*	Yes	Yes
Seizures	Yes	Yes
Stroke	Unclear	No
Anosmia	Yes	No

Abbreviations: * = unspecific and secondary to the cytokine storms/viremia, ADEM = acute disseminated encephalomyelitis, GBS = Guillan-Barré syndrome, SARS = severe acute respiratory syndrome.

Table 2. Current Practical conversion scheme from pump-based therapies to oral levodopa (based on[72])

LCIG → oral levodopa*
(ml of the morning dose x 20 - 3) + (ml/h x 20 x hours of infusion) + (ml of the extra dose x 20 x average number of extra doses/day) = total levodopa delivered in a day
LECIG → oral levodopa*
(ml of the morning dose x 20 x 1.3 - 3) + (ml/h x 20 x 1.3 hours of infusion) + (ml of the extra dose x 20 x 1.3 average number of extra doses/day) = total levodopa delivered in a day
Apomorphine → oral levodopa*
(mg of apomorphine/h x hours of infusion) x 10 = total levodopa delivered in a day

Abbreviations: * = liquid levodopa for nasogastric tube in akinetic crises can be prepared diluting 1000 mg of crushed levodopa (dispersible formulation if available) into 1000 ml of water and adding 1 gr of Vitamin C (plus domperidone in case of delayed gastric), LECIG = Levodopa Entacapone Carbidopa Intestinal Gel, LCIG = Levodopa Carbidopa Intestinal Gel.

Table 3. Current recommendations in place at Toronto Western Hospital for IPG replacement during the COVID-19 pandemic.

Recommendations for DBS patients with batteries close to end of service:

1. Alert the team and neurosurgeon's office
2. Flag high risk patients (e.g. severe dystonia in the off state, brittle PD or risk of NMS-like picture)
3. Patients should be informed that some decline of symptoms is possible, more and more as the voltage drops
4. Ask patient to monitor their controller, depending on the manufacturer:
    - Abbott/St Jude Medical (Chicago, IL, USA):
        - With 3 months or more notice for most patients, patient controller will display "Replace Generator Soon" followed by self-explanatory text advising the patient to contact the treating physician.
        - If the patient inadvertently dismisses the alert, generator status can be checked by the patient (if required) with instructions from the clinician, qualified representative or Technical helpline.
        - In the ERI period the generator status indicator on the patient controller displays a yellow triangle with an exclamation sign.
    - Boston Scientific (Valencia, CA, USA):
        - When IPG is nearing end of battery life, it will enter the elective replacement mode, i.e. stimulation continues and the remote still has some functionality but additional programming with the Clinician Programmer cannot occur.
        - Controller will alert patient displaying "ERI" (elective replacement indicator) on the screen.
        - Patients on at least 12 months of DBS will have a minimum of 4 weeks before reaching the EOS.
    - Medtronic (Dublin, Ireland):
        - Patient controller will alert patient displaying "ERI" (elective replacement indicator) on the screen when cell voltage is below 2.60V.
        - Patients will only see ERI on their remote but pressing any button they will be able to see the normal screen and interrogate the actual battery value
        - Ask patient to monitor cell voltage every 3 to 7 days, depending on energy usage
        - EOS is reached at 2.20V

Recommendations for DBS patients with IPG at end of life

1. DBS is off and remote control cannot communicate with the IPG any longer.
    - initially it might be indicated, i.e. "Replace Generator" for Abbott and "EOS" (end of service) for Boston Scientific and Medtronic devices.
2. Patients should not come to the ER but let the team know so we that the best option can be planned.
3. Most patients will eventually undergo the replacement of the IPG but – if absolutely impossible, a possible strategy would be to gradually reduce stimulation amplitude, and gradually compensate by increasing levodopa in order to avoid an acute cessation when end of IPG life is reached.

4. Other patients might only experience a mild to moderate decline of their conditions when the IPG is no longer working; in these cases some adjustments (e.g. more levodopa) can be possible to avoid an IPG replacement on an urgent basis
5. In case of life-threatening worsening of the condition, team should be informed and a request for an urgent IPG replacement should be sent.
6. Some additional precautions might be implemented (e.g. blood work and infective screening before admission)

Abbreviations: DBS = deep brain stimulation, EOS = end of service, ERI = elective replacement indicator, IPG = implantable pulse generator, NMS: neuroleptic malignant syndrome, PD: Parkinson's disease.

Table 4. Table factsheet of available software for telemedicine during COVID-19-Pandemic (modified from: Swiss Association of Physicians).

Solution	Certifications *	Mobile App	Host account required	Link (information relevant to security)
Cisco WebEx	ISO 27001 ISO 9001 ISO 27018 SOC 2 Type 2 SOC 3 FedRAMP C5: Cloud Computing Compliance Controls Catalogue Swiss Privacy Shield Frame-work certified	Yes	no	https://www.webex.com/webexremotehealth.html https://www.cisco.com/c/dam/en/us/products/conferencing/cisco-webex-security-infographic.pdf https://www.cisco.com/c/dam/en/us/products/collateral/confer-encing/webex-meeting-center/white-paper-c11-737588.pdf
Google Meet	HIPAA EU Model Contract Clauses ISO 27001 ISO 27017 ISO 27018 EY POINT SOC 1 - Type 2 SOC 2 - Type 2 SOC 3 - Type 2 FedRAMP FISC Compliance Esquema	yes	no	https://support.google.com/a/answer/7582940?hl=en https://storage.googleapis.com/gfw-touched-accounts-pdfs/google-encryption-whitepaper-gsuite.pdf https://gsuite.google.com/security/?secure-by-design_ac-tiveEl=data-centers https://cloud.google.com/security/compliance?hl=de

	Nacional de Segu-ridad (ENS)			
GoToMeeting	SOC 2 Type 2 SOC 3 C5 BSI Cloud Computing ISO 27001 AICPA`s Trust Services Criteria EU-U.S. Privacy Shield Swiss Privacy Shield	Yes	no	https://documentation.logmein.com/documentation/EN/pdf/common/LogMeIn_SecurityWhitepaper.pdf https://logmeincdn.azureedge.net/gotomeetingmedia/-/media/pdfs/ucc_security_white_paper.pdf https://www.logmeininc.com/legal/professional-services-terms
Lifesize	SOC ISO 27001 Swiss-U.S. Privacy Shield Framework	yes	yes	https://www.lifesize.com/en/solutions/industry/healthcare https://www.lifesize.com/~/media/Documents/Related%20Resources/Product%20Papers/Lifesize%20Cloud%20Security.ashx
Microsoft Teams	ISO 27001 ISO 27018 SOC 1 Type 2 SOC 2 Type 2 HIPAA FINMA HITRUST EU-US Privacy Shield Swiss-US Privacy Shield	yes	no	https://docs.microsoft.com/en-us/microsoftteams/security-com-pliance-overview https://docs.microsoft.com/en-us/microsoft-365/compliance/of-fering-eu-us-privacy-shield?view=o365-worldwide https://docs.microsoft.com/en-us/microsoftteams/teams-security-guide
Prexip	National Institutes of Stand-ards & Technology (NIST) Pexip	yes	no	https://www.pexip.com/healthcarehttps://docs.pexip.com/admin/security_best_practice.htm https://docs.pexip.com/admin/encryption_methodologies.htm

	complies with the GDPR			
Signal	Keine Angaben	yes	yes	https://www.signal.org
Skype	Swiss-US Privacy Shield	Yes	yes/no	https://support.skype.com/en/skype/all/privacy-security/ https://support.skype.com/en/faq/FA31/does-skype-use-encryp-tion https://download.skype.com/share/security/2005-031%20security%20evaluation.pdf https://privacy.microsoft.com/en-gb/privacystatement https://support.skype.com/en/faq/fa34665/try-skype-without-a-skype-account
Vidyo	ISO 9001	yes	no	https://www.vidyo.com
WhatsApp	EU-U.S. Privacy Shield Framework Swiss-U.S. Privacy Shield Framework	yes	yes	https://www.whatsapp.com/security https://www.whatsapp.com/legal/privacy-shield-addendum
Zoom	SOC 2 Type 2 TRUSTe EU-US Privacy Shield FedRAMP No Swiss-US Privacy Shield	Yes	no	https://zoom.us/security https://zoom.us/docs/doc/Zoom-Security-White-Paper.pdf

Abbreviations: * = information as from companies.

Figures Legends

Figure 1. The impact of SARS CoV-2 pandemic and Parkinson's disease on patients (modified from[20, 21]). Abbreviations: BoNT = botulinum neurotoxin. SARS CoV-2 = severe acute respiratory syndrome coronavirus 2.

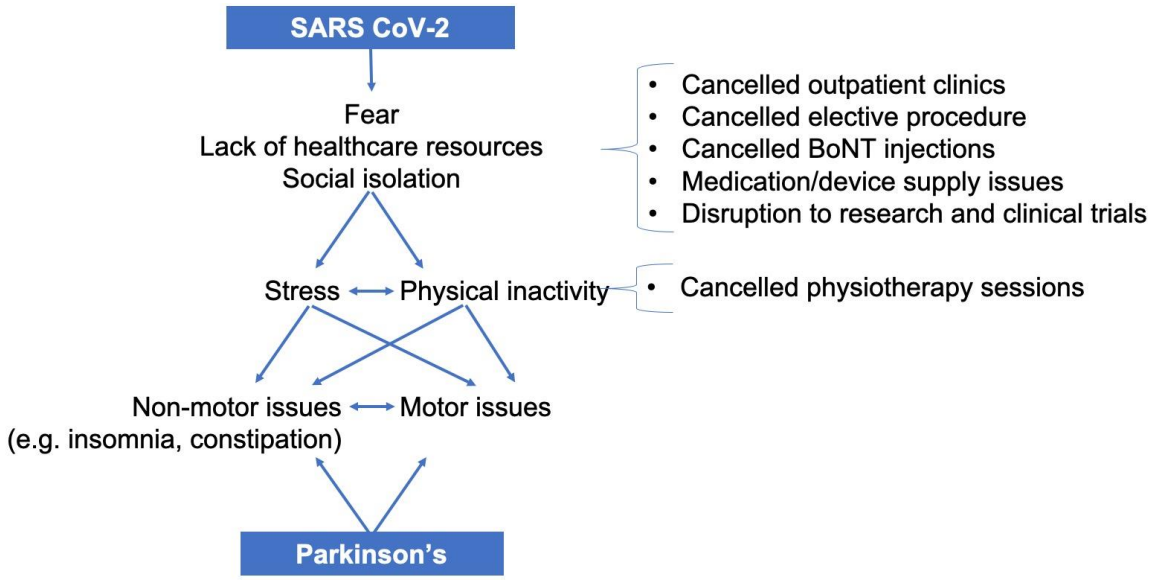

Figure 2. Triaging system for scheduled PD outpatients at Toronto Western Hospital during the SARS CoV-2 pandemic. Abbreviations: PD = Parkinson's disease, SARS CoV-2 = severe acute respiratory syndrome coronavirus 2.

Figure 3. Examples of telemedicine assessment in a LCIG patient showing the status of PEG (A), DBS patient changing stimulating parameters on her controller to improve gait (B) and a patient recently operated with DBS to assess the status of the surgical wounds. Abbreviations: DBS = deep brain stimulation, LCIG = levodopa-carbidopa intestinal gel, PEG = percutaneous endoscopic gastrostomy.