Moving Forward from the COVID-19 Pandemic: Needed Changes in Movement Disorders Care and Research

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Abstract
Purpose of Review The COVID-19 pandemic has dramatically affected the health and well-being of individuals with movement disorders. This manuscript reviews these effects, discusses pandemic-related changes in clinical care and research, and suggests improvements to care and research models.

Recent Findings During the ongoing COVID-19 pandemic, individuals with movement disorders have experienced worsening of symptoms, likely due to decreased access to care, loss of social connection, and decreased physical activity. Through telemedicine, care has moved out of the clinic and into the home. Clinical research has also been significantly disrupted, and there has been a shift to decentralized approaches. The pandemic has highlighted disparities in access to care and representation in research.

Summary We must now translate these experiences into better care and research models with a focus on equitable integration of telemedicine, better support of patients and caregivers, the development of meaningful digital endpoints, and optimization of decentralized research designs.

Keywords Telemedicine · Decentralized research · Digital health tools · Social connection · Parkinson’s disease

Introduction

The COVID-19 pandemic has claimed the lives of over 5 million people [1] and changed the way we practice medicine and conduct research. To mitigate the risk of infection, a wide range of protective measures, including physical distancing, masking, closures of businesses and services, and stay-at-home orders, have been put in place at various points during the pandemic. During this tumultuous and stressful time, many people living with movement disorders like Parkinson’s disease (PD) have experienced a decline in their health and have had difficulty accessing care. The medical community has responded to this crisis in management of chronic neurological diseases through the widespread implementation of telemedicine, a term that is used here to refer to synchronous, video-based visits for the provision of medical care. The care of individuals with movement disorders, who may have difficulty traveling to in-person visits due to disability, is well-suited to telemedicine. In contrast to some other neurological disorders, the movement disorders examination is primarily visual in nature. The research community has responded similarly by moving research out of the clinic and into the home.

While there are now multiple, highly effective vaccines [2–5], low vaccination rates in some regions and lack of availability of vaccines in other regions have prolonged the pandemic [6]. Neither clinical care nor research have returned to their pre-pandemic state. Here, we review the impact of the pandemic on people living with movement disorders; discuss lessons learned regarding the importance of social connection, exercise, and access to care; and review changes in the clinical research landscape. Now is the time to re-imagine care and research. We propose changes to optimize care and research models to withstand the effects of current and future pandemics.
Impact of the pandemic on individuals with movement disorders

The COVID-19 pandemic has significantly impacted the daily lives of those with PD, limiting access to medical care and disrupting routine activities [7•]. Almost overnight, individuals were unable to attend in-person clinic visits, support groups, exercise programs, or religious services and unable to see family members or engage in social activities. Several studies from across the globe have demonstrated that individuals with PD have experienced worsening of symptoms during the pandemic. Symptomatic worsening was reported by 38.5% in a study in India (n = 832) [8], by more than 50% in a study in Brazil (n = 478) [9], and by 65.7% in a study in Spain (n = 568) [10]. In a study with largely US-based respondents (n = 5249), worsening of motor symptoms was reported by 43% and worsening of non-motor symptoms by 52% [7•]. PD psychiatric symptoms in particular have been noted to worsen with studies identifying increases in impulse control behaviors [11], worsening of anxiety and depressive symptoms [12], and a higher prevalence of anxiety and depression [13, 14].

Similarly, the pandemic has negatively affected individuals living with other movement disorders. Reports describe worsening of motor and non-motor symptoms among those with multiple system atrophy [15] and those with dystonia [16, 17]. In a study of individuals with Tourette’s syndrome and chronic tic disorders, there was an overall reduction in tic severity but increase in psychiatric symptoms [18]. Interestingly, in two studies, functional movement disorder motor symptoms did not appear to worsen although individuals experienced worsening of mood and sleep symptoms [19, 20]. Contrasting these findings, others have described a marked increase in new referrals for functional tic-like behaviors [21].

Decreased access to medical care may provide a partial explanation for the worsening of symptoms experienced by individuals with movement disorders. In a large, survey-based study, the majority of people with PD (64%) reported disruptions in their medical care during the pandemic [7•]. During the early phase of the pandemic, there was decreased access to care for management of deep brain stimulation [22], botulinum toxin injections [17], and initiation of levodopa-carbidopa intestinal gel and continuous subcutaneous apomorphine infusion [23]. These disruptions extended to rehabilitative therapies; in one survey-based study, 60% of individuals with PD lost their access to rehabilitative care [12]. In a qualitative study, many individuals with PD reported feeling alone and unsupported during the pandemic due to limited communication with their providers [24]. Access to treatment was not uniformly disrupted. Non-white individuals and those from lower socioeconomic status reported more difficulty in obtaining PD medications [7•]. Similar trends were seen when comparing high-income countries to low-income countries; 89% of movement disorders providers in low-income countries reported that their patients with PD had difficulty accessing medications during the COVID-19 pandemic versus 23% of providers in high-income countries [25].

These disruptions in care impacted well-being. Those who had disruptions in their PD care or access to medications were more likely to experience symptomatic decline or increased disability [7•, 25]. Patient-reported difficulties with deep brain stimulation devices predicted worsened symptoms [22]. In another study, one-third of those who reported worsening of PD symptoms associated this with loss of rehabilitative care [12]. However, disruptions in medical care do not provide a full explanation for changes in well-being. Multiple other reasons have been postulated including psychological distress, decreased physical activity, fewer social contacts, loneliness, and isolation [7•, 24, 26, 27•]. Loneliness and isolation are associated with increased PD symptom severity and decreased quality of life [27•]. Pandemic-related restrictions have made it more difficult to maintain social connections. The need to isolate or quarantine, prolonged home confinement, insufficient home support, and disruptions in social activities during the pandemic have been associated with worsening or emergence of PD symptoms [7•, 8]. In a retrospective analysis (n = 264), worsened motor progression was observed during a period of lockdown during which the mean levodopa equivalent dose was unchanged; the authors hypothesized that social isolation and decreased physical activity were responsible [28]. Several studies have identified an association between reduced levels of physical activity and worsening of a variety of PD symptoms [7•, 9, 26, 29•, 30]. In a study in India, maintaining an adequate level of physical activity was associated with a lower likelihood of new or worsened sleep problems [31].

Caregivers have also been impacted by the pandemic, in part due to decreased access to community-based programs and home health services [32]. In one study, 26% of caregivers for individuals with PD reported increased caregiver burden in the setting of the COVID-19 lockdown [33]. In another study, more than 50% of caregivers for individuals with PD reported worsened stress levels in the setting of pandemic-related home confinement [30]. Similarly, among caregivers for individuals with multiple system atrophy, anxiety has been commonly reported during the pandemic [15]. During the pandemic, increased caregiver strain was associated with higher burden of non-motor symptoms [30] and higher levels of disability [34] in individuals with PD.
Changes in care in response to the pandemic

At the beginning of the COVID-19 pandemic, clinics quickly transitioned from in-person visits to telemedicine and there was a global increase in the use of telemedicine in movement disorders [35]. The rapid implementation and widespread shift to telemedicine represented a major change in healthcare delivery in movement disorder clinics. In the USA, this was facilitated by policy changes that eased existing telemedicine restrictions, introduced pay parity, and allowed for flexibility in platform selection [36]. Professional organizations, including the Movement Disorder Society and American Academy of Neurology, released guidelines to facilitate the transition to telemedicine [37, 38]. Telemedicine use among individuals with PD increased from 9.7% prior to the pandemic to 63.5% during the pandemic [39•]. Even management of advanced therapies [40] and evaluation of candidacy for deep brain stimulation shifted to telemedicine [41]. In response to the need, telerehabilitation similarly expanded with virtual physical therapy visits, recorded on-demand exercise classes, and smartphone applications [24, 42•]. One group even noted an unexpected increase in recruitment for their PD virtual exercise program during the pandemic [43]. As a community, we quickly learned that many aspects of care for individuals with movement disorders can be delivered remotely.

The COVID-19 pandemic also served to highlight disparities in care among underserved populations. Substantial disparities in neurologic healthcare access and utilization exist in the USA. Prior to the COVID-19 pandemic, one study found that Hispanic patients were 40% less likely and Black patients 30% less likely than white patients to see an outpatient neurologist [44]. Similarly, minorities with PD had lower rates of referrals to a specialist compared to white men [45]. Before the pandemic, newly diagnosed Black patients were four times less likely than white patients to receive treatment after initial diagnosis (12% vs 38%) [46]. The shift to telemedicine has exacerbated disparities in access to care. In a survey of individuals with PD, telemedicine use was highest among those with higher incomes, those with higher levels of education, and white individuals [39•]. Similarly, an academic movement disorders center found that the percentage of telemedicine visits compared to in-person visits prior to the pandemic increased for white patients and decreased for Black patients suggesting decreased uptake of telemedicine among Black patients [47].

Other changes in care focused on the need to bolster support for individuals, provide opportunity for social connection, and encourage exercise. For example, one clinic sought, in conjunction with a PD advocacy organization, to tackle the social isolation and strain on caregivers with virtual support groups [48•]. At the University of Rochester, we successfully transitioned our Huntington’s disease support groups and educational events to a virtual format. Another clinic developed a targeted COVID-19 outreach program for their homebound patients with advanced parkinsonism [49]. In the setting of the closure of physical exercise spaces and classes, patients found alternative means of activity, including walking around their communities, home DVD exercise programs, and virtual exercise classes. Non-profit organizations, like the Parkinson’s Foundation, helped fill resource gaps by bolstering existing and creating new virtual programs [50].

Future directions in clinical care

The COVID-19 pandemic has exposed the flaws in our medical systems and forced us to re-consider the way that we practice medicine. Now is the time to re-imagine the way that we provide care (Table 1). Telemedicine has become integral to the care of individuals with movement disorders. Flexibility in visit type represents a patient-centered approach to providing care and should be maintained. To ensure the long-term viability of telemedicine, we must optimize care models, enact permanent policy changes to minimize regulatory and reimbursement barriers, and address disparities in telemedicine use. More work is needed to identify the best models for the delivery of coordinated interdisciplinary care that incorporates telemedicine and optimizes the experience of telemedicine. Additionally, the pandemic has highlighted the need for more readily available technology to support remote deep brain stimulation programming [40, 57], an option that only recently became available in the USA, and remote options for the management of medication pumps.

While telemedicine has helped many patients with movement disorders receive care during the pandemic, the shift to telemedicine has also amplified existing health disparities. Disparities in access to care are driven in part by the presence of a digital divide. The digital divide is the gap between individuals who have access to digital technologies and the necessary digital literacy to use them and those who do not. In the USA, approximately 18 million Americans do not have Internet access according to the Federal Communications Commission [58] and about 25% of Americans may not have digital literacy skills [59••]. Only 57% of adults with lower incomes have home broadband services compared to 93% of adults with higher incomes [60]. According to a 2021 Pew Research Center survey, Black and Hispanic individuals in the USA are less likely to own a computer and have home broadband access [61]. The survey found that 80% of white individuals have a broadband connection at home compared to 71% of Black individuals and 65% of Hispanic individuals [61].

In order to optimize the use of telemedicine among underserved groups and ensure equitable access, we need to make
**Table 1** Recommendations for optimizing the care of individuals with movement disorders

| Goal | Benefits | Barriers |
|------|----------|----------|
| Integration of telemedicine into care models | • Improves access to care | • Licensing restrictions |
| | • Increases convenience and comfort | • Absence of regulations guaranteeing permanent payment parity |
| | • Reduces risk of communicable disease | • Need for new support roles within the medical system |
| | • Enables continuity of care | • Disparities in access |
| | • Reduces geographic barriers | • Lack of widespread affordable broadband internet |
| | • Enables care partners and family members to participate | • Lack of device ownership |
| | • Improves access to rehabilitative therapies | • Limited digital literacy |
| | • Potential to reach underserved populations | • Inability to manage advanced therapies |
| Holistic support of patients | • Connection with needed social services improves health outcomes | • Absence of appropriate financial models to support this work |
| | • Exercise improves symptom management | • Insufficient community resources |
| | • Social connection may improve health outcomes | • Need for research on effective models |
| | • Self-management skills enhance quality of life | • Lack of financial support |
| Robust support for care partners | • Improves quality of life for individuals with movement disorders | • Caregiver burnout |
| | • Reduces caregiver burden | • Insufficient community resources |
| | • Reduces strain on healthcare system | |

a unified effort to dismantle barriers. At the department and institution level, we recommend systematically tracking use of telemedicine to identify disparities in use, developing and implementing targeted strategies to address any identified disparities, and assessing the impact of these interventions. Strategies may include the development or strengthening of community partnerships, education and training, and improved access to language services. For example, establishing partnerships with community centers that can provide computers, Internet connections, and private locations may facilitate access and improve patient comfort with telemedicine visits. The distribution of written or online materials, direct engagement by clinical staff, and education of family members may improve digital literacy and help ensure successful telemedicine visits. For patients where English is not their primary language, it is important to provide health services in their language. This can be done by connecting patients with clinicians that also speak their language or by using interpreter services. For example, one of the authors opened a Spanish language neurology clinic to improve access to quality neurologic care to the Hispanic community in the surrounding region. Policy changes are also critical to address disparities in access. We recommend on-going advocacy for affordable, home broadband access for all. We also recognize the value of audio-only (telephone) visits as an adjunct to in-person care for those unable to complete telemedicine visits and recommend on-going advocacy for pay parity for these visits.

Our care of patients does not end when they leave the office (or the video visit). Nor should it be limited to addressing medical issues. The pandemic has highlighted the importance of social connection and physical activity in overall well-being. As clinicians, we must be at the forefront of helping patients maintain connection, remain physically active, and access needed social services. Social prescribing, which involves connecting individuals with non-medical services, represents one strategy for improving overall health. Examples of social prescribing that may help to improve social connection include programs such as the Togetherness Program at CareMore and the Veteran’s Administration Compassionate Contact Corps Program, which involve proactive phone calls/visits to isolated patients. We must support research into social prescribing and advocate for policy changes to ensure adequate community supports. Additionally, optimization of virtual support groups may help to improve social connection of patients and caregivers. We must also help patients and caregivers build their armamentarium of self-management tools and skills. This may include developing programs to help patients strengthen coping strategies, manage anticipatory grief, adapt their lifestyles to changes from PD, enhance adherence to medical treatment, and process emotions resulting from living with a chronic disease. Targeted education for caregivers may improve self-management and self-efficacy, as well.

Caregivers in the USA provided approximately $470 billion worth of unpaid services in 2013, averaging 20 h of caregiving per week. Caregivers have a positive impact on individuals with PD, who experience improved quality of life and reduced spiritual distress, both vital during situations like the COVID-19 pandemic. We must provide better support for unpaid caregivers.
of programs such as the National Family Caregiver Support Program and state-run consumer-directed home care programs, which strive to help individuals remain in their homes with additional supportive services including pay for family caregivers [63, 65], may help to reduce caregiver burden and improve patient quality of life.

Research

Long before the global COVID-19 pandemic, it was clear that new research models were needed as few drugs that entered phase I trials for central nervous system disorders ultimately obtained regulatory approval [66]. One of the barriers to successful and efficient drug approval is clinical trial recruitment, and many clinical trials fail to meet enrollment targets on time [67]. Barriers to research participation are numerous and include burdensome financial, travel, and caregiver requirements [68] that may be particularly problematic for individuals with progressive neurodegenerative disorders characterized by mobility difficulties and cognitive impairment.

At the start of the pandemic, non-COVID-19 clinical research in many regions was suspended [69]. In a survey of a large PD research network in North America, the majority of respondents reported significant disruptions in research activities; 90% reported disruptions in recruitment, 79% suspension of new studies, and 35% closure of their research center [70•]. The US Food and Drug Administration [71] and the European Medicines Agency [72] issued guidance documents on the safe conduct of clinical trials during the COVID-19 pandemic that covered such topics as the use of remote (telephone or video-based) visits, home delivery of study drug, and remote data collection. While clinical research has since re-started, it continues to be impacted by the cycle of restrictions and easements that has typified this pandemic, and by downstream effects of the pandemic, such as staffing shortages [73]. We are now faced with the challenge of re-designing clinical research to mitigate the effects of current and future pandemic-related disruptions. In doing so, we also have the opportunity to re-center the patient in clinical research and improve the clinical research process (Fig. 1).

Decentralized studies flip the traditional research structure and move the conduct of research out of the clinic and into the home. This may involve, for example, remote assessment via real-time video-conferencing (video visits), obtainment of real-world data using digital devices, in-home safety assessment or collection of biological specimens, or home delivery of study drug. During the pandemic, remote observational studies of LRRK2 carriers and PD clinical trial participants continued without interruption [74, 75]. These studies utilized a small team of coordinators and investigators to enroll and characterize participants from across the USA, irrespective of their proximity to specialized research centers, by using video visits and common outcome measures [76]. Such video visits are well-liked by participants, offering comfort and convenience, as they eliminate the need for travel and reduce the burden on participants [77]. However, simply replicating what we do with in-person visits fails to realize the potential of video visits [68], which may enable new, previously unmeasurable insights.

Digital devices, such as smartphones and wearable sensors, enable the real-world collection of massive amounts of data and can provide unique insights into the lived experience. Digital devices can be used to measure a variety of motor constructs, including gait [78], tremor [79], bradykinesia [80], and chorea [81] outside of the clinic. They can detect change in response to PD medication treatment [82], be used to monitor falls [83], and may be able to predict future clinical outcomes [84]. While the digital assessment of non-motor features is less developed, digital devices can, for example, capture sleep parameters [85], skin temperature [86], and blood pressure [87]. During the pandemic, smartphone applications have successfully been used to remotely monitor patients with PD [88] and remotely capture clinical trial outcomes [89]. Yet few clinical trials use digital endpoints [90], and more work is needed to create holistic, patient-centered, and clinically meaningful measures. Highlighting the need for clinically relevant digital endpoints, the US FDA recently rejected applications for the MC10 BioStamp nPoint® Huntington’s disease gait assessment and the Verily Study Watch Parkinson’s disease motor assessment raising questions regarding the ability for these tools to assess meaningful functional change [91, 92].
Future Directions in Research

While decentralized studies eliminate some barriers to research participation, they have not addressed the critical problem of underrepresentation in research studies. Without adequate representation, we cannot fully understand disease [93•] or the safety and efficacy of treatments [94]. Black and Hispanic individuals are under-represented in PD clinical trials [95] and recent PD decentralized studies have failed to recruit representative samples [76]. While decentralized studies reduce transportation-related barriers to participation, they may impose new barriers to research participation. As noted above, Black and Hispanic individuals are less likely to have access to home broadband compared to white individuals [61]. Without concerted action, this digital divide threatens to worsen the issue of representation in research. As a research community, we need to prioritize inclusivity and devote the necessary resources and funds to tackling this problem. Strategies may include partnering with trusted community organizations and advocates, providing study materials in languages other than English, ensuring a diverse research team [68], providing training on inclusive research practices [93•], educating community providers on research opportunities [96], and providing the technology required for participation. We cannot assume that recruitment strategies designed for traditional in-person studies will translate to decentralized studies [76]. Future work should focus on the development of strategies to enhance diversity and inclusion within decentralized research studies.

More work is needed to optimize decentralized clinical research designs and identify meaningful digital endpoints. The barriers to incorporating digital devices in clinical research studies are numerous. Among others, the barriers include the complexity and sheer amount of raw data, challenges in validation, concerns regarding adherence, acceptability to regulatory agencies, constantly changing technology, and challenges integrating data [97]. Pre-competitive collaborations, such as those led by the Digital Medicine Society and Critical Path for Parkinson’s, may help to streamline and efficiently advance the development of new digital tools and endpoints [97]. Patient involvement, early and often, in the development of digital assessments will be critical to ensure the selection of meaningful outcome measures. While in many ways less complex than digital devices, we must not ignore the many other facets of decentralized clinical research. For example, we must eliminate barriers to the use of video visits and devote resources towards the standardization and validation of assessments for video visits. To reduce barriers to use, regulatory agencies must align around guidelines for the conduct of video visits and sponsors must commit the necessary funds and personnel support [98]. We should also build flexibility (e.g., in regard to visit location or method of obtaining informed consent) into our study designs [99]. Such planned flexibility is more participant-centric and will allow us to much more readily adapt to future unexpected challenges in clinical research conduct. This flexibility should extend to how and where we capture outcomes. Not all studies will be appropriate for a fully decentralized approach and hybrid studies that include in-person assessments may offer the best of both worlds—the ability to capture real-world outcomes and to collect biological and neuroimaging data.

Conclusions

The COVID-19 pandemic has dramatically affected those living with movement disorders, highlighted faults in our systems, and likely permanently altered the way we provide care and conduct research. We must now focus on creating more robust healthcare systems by optimizing interdisciplinary care models that incorporate telemedicine, developing ways to remotely manage advanced therapies, building clinical programs that foster development of self-management skills and provide social supports, and expanding support of caregivers. We should embrace patient-centered decentralized clinical research designs and focus on developing or optimizing the practices and technologies that make such research possible. All of these efforts need to be performed with a focus on equity and inclusivity.

Declarations

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

● Of importance

● Of major importance

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/ Accessed November 16th, 2021.
2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurttman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA
Covid-19 Vaccine. N Engl J Med. 2020;383:2603–15. https://doi.org/10.1056/NEJMoA2034577.

3. Voysey M, Clemens SAC, Madhi SA, Lily WY, Folegatti PM, Aley PK, et al. Safety and efﬁcacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397:99–111. https://doi.org/10.1016/S0140-6736(20)32661-1.

4. Baden LR, El Sahly HM, Essink B, Kotoff K, Frey S, Novak R, et al. Efﬁcacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403–16. https://doi.org/10.1056/NEJMa2035389.

5. Sadoff J, Gray G, Vandenbosh A, Cárdenas V, Shukarev G, Grinstein B, et al. Safety and efﬁcacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. 2021;384:2187–201. https://doi.org/10.1056/NEJMoA2101544.

6. World Health Organization. Vaccine uptake per 100 population. https://app.powerbi.com/view?r=eeyJrJloMWNjNzZkJcZTZNiN00YmZlTkZjQ0NuiZ2DM2MTYxNzEwiwCICmCY2MTBjMGl3LWJkJmQtNjNGLoOS04MTBjLTNjNYz14MGFmYjU5CIhIMi0j9 Accessed December 6th, 2021.

7. Brown EG, Chahine LM, Goldman SM, Korell M, Mann E, Kinel DR, et al. The effect of the COVID-19 pandemic on people with Parkinson’s disease. J Parkinsons Dis. 2020;10:1356–77. https://doi.org/10.3233/JPD-202249. Identifies that the COVID-19 pandemic created signiﬁcant disruptions in PD care, that were more common among non-white individuals and those from lower socioeconomic status.

8. Kumar N, Gupta R, Kumar H, Mehta S, Rajan R, Kumar D, et al. Impact of home conﬁnement during COVID-19 pandemic on Parkinson’s disease. Parkinsonism Relat Disord. 2020;80:32–4. https://doi.org/10.1016/j.parkreldis.2020.09.003.

9. Silva-Batista C, Coelho DB, Júnior RCF, Almeida LR, Guimarães A, Nóbrega KCC, et al. Multidimensional factors can explain the clinical worsening in people with Parkinson’s disease during the COVID-19 pandemic: a multicenter cross-sectional trial. Front Neurol. 2021;12:708433. https://doi.org/10.3389/fneur.2021.708433.

10. Santos-García D, Oleiro M, Pérez P, Fanjul G, González JMP, Painceiras MJF, et al. Impact of coronavirus disease 2019 pandemic on Parkinson’s disease: a cross-sectional survey of 568 Spanish patients. Mov Disord. 2020;25(35):1712–6. https://doi.org/10.1002/mds.20261.

11. Yule E, Pickering JS, McBride J, Poliakoff E. People with Parkinson’s report increased impulse control behaviors during the COVID-19 UK lockdown. Parkinsonism Relat Disord. 2021;86:38–9. https://doi.org/10.1016/j.parkreldis.2021.03.024.

12. Yoget-Seligmann G, Kafri M. COVID-19 social distancing: negative effects on people with Parkinson disease and their associations with conﬁdence for self-management. BMC Neurol. 2021;21:284. https://doi.org/10.1186/s12883-021-02313-6.

13. Salari M, Zali A, Ashraﬁ F, Etemadifar M, Sharma S, Hajizadeh N, et al. Incidence of anxiety in Parkinson’s disease during the coronavirus disease (COVID-19) pandemic. Mov Disord. 2020;35:1095–6. https://doi.org/10.1002/mds.28261.

14. Kitani-Morii F, Kasai T, Horiguchi G, Teramukai S, Ohmichi T, Shimomoto M, et al. Risk factors for neuropsychiatric symptoms in patients with Parkinson’s disease during COVID-19 pandemic in Japan. PLoS One. 2021;16:e0245864. https://doi.org/10.1371/journal.pone.0245864.

15. Cámaras A, Compta Y, Pèrez-Soriano A, Montagut N, Baixauli M, Maragall L, et al. Effects of COVID-19 pandemic and lockdown on people with multiple system atrophy participating in a therapeutic education program. Parkinsonism Relat Disord. 2021;86:78–80. https://doi.org/10.1016/j.parkreldis.2021.03.021.

16. Delgado C, Paréès I, Kurth MM. Patients’ perspective of dystonia symptoms during the SARS-CoV-2 pandemic. Mov Disord. 2021;36:1485–6. https://doi.org/10.1002/mds.28645.

17. Dressler D, Saberi FA. Botulinum toxin therapy in the SARS-CoV-2 pandemic: Patient perceptions from a German cohort. J Neurol Transm (Vienna). 2020;127:1217–4. https://doi.org/10.1007/s00702-020-02235-6.

18. Graziofi P, Garone G, Criscolo LD, Grasso M, Curatolo P, Vige vano F, et al. Impact of Italian lockdown on Tourette’s syndrome patients at the time of the COVID-19 pandemic. Psychiatry Clin Neurosci. 2020;74:610–2. https://doi.org/10.1111/pcn.13131.

19. Delgado C, Paréès I, Jiménez-Huete A, Kurth MM. Impact of the coronavirus disease 2019 pandemic on functional movement disorders: lessons from a specialized clinic. Mov Disord. 2020;35:1723–4. https://doi.org/10.1002/mds.28278.

20. Nisticò V, Goeta D, Gambini O, Demartini B. The psychological impact of COVID-19 among a sample of Italian patients with functional neurological disorders: a preliminary study. Parkinsonism Relat Disord. 2020;78:79–81. https://doi.org/10.1016/j.parkreldis.2020.07.019.

21. Pringshimes R, Ganos C, McGuire JF, Hedderly T, Woods D, Gilbert DL, et al. Rapid onset functional tic-like behaviors in young females during the COVID-19 pandemic. Mov Disord. 2021. https://doi.org/10.1002/mds.28778.

22. Piano C, Bove F, Tufo T, Imbimbo I, Genovese D, Stefani A, et al. Effects of COVID-19 lockdown on movement disorders patients with deep brain stimulation: a multicenter study. Front Neurol. 2020;11:616550. https://doi.org/10.3389/fneur.2020.616550.

23. Richter D, Scherbaum R, Bartig D, Gold R, Krogias C, Tönges L. Analysis of nationwide multimodal complex treatment and drug pump therapy in Parkinson’s disease in times of COVID-19 pandemic in Germany. Parkinsonism Relat Disord. 2020;85(2):109–13. https://doi.org/10.1016/j.parkreldis.2020.03.006.

24. Angeleseucu BA, Bruno V, Martino D, Roach P. Effects of the COVID-19 pandemic on Parkinson’s disease: a single-centered qualitative study. Can J Neurol Sci. 2021;1:1–13. https://doi.org/10.1017/cjn.2021.70.

25. Cheong JL, Goh ZHK, Marra H, Tanne M, Kasten N, Noyce A, et al. The impact of COVID-19 on access to Parkinson's disease medication. Mov Disord. 2020;35:2129–33. https://doi.org/10.1002/mds.28293.

26. van der Heide A, Meinders MJ, Bloem BR, Helmich RC. The impact of the COVID-19 pandemic on psychological distress, psychical activity, and symptom severity in Parkinson’s disease. J Parkinsons Dis. 2020;10:1355–64. https://doi.org/10.3233/JPD-202251.

27. Subramanian I, Farahnik I, MischleyLK. Synergy of pandemics – social isolation is associated with worsened Parkinson severity and quality of life. NPJ Parkinsons Dis. 2020;6:28. https://doi.org/10.1038/s41531-020-00128-9. Highlights the association between social isolation and worse quality of life among individuals with PD, proposes strategies for increasing social engagement, and calls for more research in this area.

28. Ineichen C, Baumann-Vogel H, Sitzler M, Walkdvoelc D, Bau mann CR. Worsened Parkinson’s disease progression: Impact of the COVID-19 pandemic. J Parkinsons Dis. 2021;11:1579–83. https://doi.org/10.3233/JPD-212779.

29. Song J, Ahn JH, Choi I, Mun JK, Cho JW, Youn J. The changes of exercise pattern and clinical symptoms in patients with Parkinson’s disease in the era of COVID-19 pandemic. Parkinsonism Relat Disord. 2020;80:148–51. https://doi.org/10.1016/j.parkreldis.2020.09.034. Highlights the association between reduced amount, duration, and frequency of exercise among individuals with PD during the COVID-19 pandemic and increased motor and non-motor symptoms.
30. Oppo V, Serra G, Fenu G, Murgia D, Ricciardi L, Melis M, et al. Parkinson’s disease symptoms have a distinct impact on caregivers’ and patients’ stress: a study assessing the consequences of the COVID-19 lockdown. Mov Disord Clin Pract 2020;7:865-867. https://doi.org/10.1002/mdc3.13030.

31. Kumar N, Gupta R, Kumar H, Mehta S, Rajan R, Kumar D, et al. Impact of home confinement during COVID-19 pandemic on sleep parameters in Parkinson’s disease. Sleep Med. 2021;77:15-22. https://doi.org/10.1016/j.sleep.2020.11.021.

32. Macchi ZA, Ayele R, Dini M, Lamira J, Katz M, Pantilat SZ, et al. Lessons from the COVID-19 pandemic for improving outpatient neuropsychiatric care: a qualitative study of patient and caregiver perspectives. Palliat Med. 2021;35:1258–66. https://doi.org/10.1177/02692161211017383.

33. Basch R, et al. Changes in motor, cognitive, and behavioral symptoms in Parkinson's disease and mild cognitive impairment during the COVID-19 lockdown. Front Psychiatry. 2020;11:590134. https://doi.org/10.3389/fpsyt.2020.590134.

34. De Micco R, Siciliano M, Sant’Elia V, Giordano A, Russo A, Tedeschi G, et al. Correlates of psychological distress in patients with Parkinson’s disease during the COVID-19 outbreak. Mov Disord Clin Pract. 2020;8:60–8.

35. Hassan A, Mari Z, Gatto EM, Cardoza A, Youn J, Okubadejo N, et al. Global survey on telemedicine utilization for movement disorder patient care. MDS Journal of Parkinson's Disease. 2020;10:1383–8. https://doi.org/10.3233/JPD-202156.

36. Larson DN, Schneider RB, Simuni T. A new era: the growth of telemedicine and remote care. Mov Disord Clin Pract. 2020;8:1212–19. https://doi.org/10.1002/mdc3.12994.

37. American Academy of Neurology. Telemedicine and COVID-19 implementation guide. Updated April 10, 2020. https://www.aan.com/ sites/ assets/ home-page/ tools-and-resources/ practice-ice- neurologist—administrators/ telemedicine-and-remote-care/20-telemedicine-and-covid-19-v103.pdf Accessed December 6th, 2021.

38. International Parkinson and Movement Disorder Society. Telemedicine in your movement disorders practice. https://www.movementdisorders.org/MDS/About-Committees—Other-Groups/Telemedicine-in-Your-Movement-Disorders-Practice-A-Step-by-Step-Guide.htm Accessed December 6th, 2021.

39. Feeney MP, Xu Y, Surface M, Shah H, Vanegas-Arroyave N, Chan AK, et al. The impact of COVID-19 and social distancing on people with Parkinson's disease: a survey study. NPJ Parkinsons Dis. 2021;7:10. https://doi.org/10.1038/s41531-020-00153-8.

40. Fasano A, Antonini A, Katzenschlager R, Krack P, Odin P, Evans AH, et al. Management of advanced therapies in Parkinson's disease patients in times of humanitarian crisis: The COVID-19 experience. Mov Disord Clin Pract. 2020;7:361–72. https://doi.org/10.1002/mdc3.12965.

41. York MK, Farace E, Pollak L, Floden D, Lin G, Wyman-Chick K, et al. The global pandemic has permanently changed the state of practice for pre-DBS neuropsychological evaluations. Parkinsonism Relat Disord. 2021;86:135–8. https://doi.org/10.1016/j.parkreldis.2021.04.029.

42. Langer A, Gassner L, Flotz A, Hasenauer S, Gruber J, Wizany L, et al. How COVID-19 will boost remote exercise-based treatment in Parkinson’s disease: a narrative review. NPJ Parkinsons Dis. 2021;7:25. https://doi.org/10.1038/s41531-021-00160-3.

43. Provides an overview of current telerehabilitation options for patients with Parkinson’s disease.

44. Quinn L, Macpherson C, Long K, Shah H. Promoting physical activity via telehealth in people with Parkinson disease: the path forward after the COVID-19 pandemic? Phys Ther. 2020;100:1730–6. https://doi.org/10.1093/ptj/pzaa128.

45. Willis AW, Schootman M, Evanoff BA, Perlmutter JS, Racette BA. Neurololgist care in Parkinson disease: A utilization, outcomes, and survival study. Neurology. 2011;77:851–7.

46. Dahodwala N, Xie M, Noll E, Siderowf A, Mandell DS. Treatment disparities in Parkinson’s disease. Ann Neurol. 2009;66(2):142–5. https://doi.org/10.1002/ana.21774.

47. Esper CD, Scorr L, Papazian S, Bartholomew D, Esper GJ, Factor SA. Telemedicine in an academic movement disorders center during COVID-19. J Mov Disord. 2021;14:119–25. https://doi.org/10.14802/jmd.20099.

48. Subramanian I. Virtual Parkinson’s disease support groups in the COVID-19 era: Social connection in the time of social distancing. Mov Disord Clin Pract. 2020;7:739–40. https://doi.org/10.1002/mdc3.12994.

49. Sennott B, Wee K, Hess S, Mitchem D, Klostermann EC, Myrick E, et al. Novel outreach program and practical strategies for patients with parkinsonism in the COVID-19 pandemic. J Parkinsons Dis. 2020;10:1383–8. https://doi.org/10.3233/JPD-202156.

50. Parkinson’s Foundation. PD Health @ Home. https://www.parkinsons.org/Living-with-Parkinsons/Resources-and-Support/PD-Health-at-Home Accessed December 6th, 2021.

51. Dorsey ER, Okun MS, Bloem BR. Care, convenience, confidentiality, and contagion: the 5 Cs that will shape the future of telemedicine. J Parkinsons Dis. 2020;10(3):893–7. https://doi.org/10.3233/JPD-202109.

52. Beck CA, Beran DB, Biglan KM, Boyd CM, Dorsey ER, Schmidt PN, et al. National randomized controlled trial of virtual house calls for Parkinson disease. Neurology. 2017;89(11):1152–61. https://doi.org/10.1223/WNL.0000000000004357.

53. Lyles CR, Wachter RM, Sarkar U. Focusing on Digital Health and telemedicine for chronic disease management during the Covid-19 pandemic. NEJM Catal Innov Care Deliv. 2020. https://doi.org/10.1056/jcatal.2020.07.003.

54. Alderwick HA, Gottlieb LM, Fichtenberg CM, Adler NE. Social prescribing in the U.S. and England: emerging interventions to address patients’ social needs. Am J Prev Med. 2018;54:715–8. https://doi.org/10.1016/j.amepre.2018.01.039.

55. Duits AA, Boots LMM, Mulders AEP, Moonen AJH, Vugt ME. Covid proof self-management training for caregivers of patients with Parkinson’s disease. Mov Disord. 2021;36:529–30. https://doi.org/10.1002/mds.28457.

56. Prizer LP, Kluger BM, Sillau S, Katz M, Galifianakis NB, Miyasaki JM. The presence of a caregiver is associated with patient outcomes in patients with Parkinson’s disease and atypical parkinsonisms. Parkinsonism Relat Disord. 2020;78:61–5. https://doi.org/10.1016/j.parkreldis.2020.07.003.

57. Xu J, Wang J, Keith S, Zhang M, Yang C, Yuan Q, et al. Management of Parkinson’s disease patients after DBS by remote programming: preliminary application of single center during quarantine of 2019-nCoV. J Neurol. 2021;268:1295–303. https://doi.org/10.1007/s00415-020-10273-9.

58. Prizer CP, Henderson MD,戣 HI, Kwon O, Cheng F, et al. Remote therapy for Parkinson disease in the COVID-19 era. J Park Relat Disord. 2020;66(2):142–5. https://doi.org/10.1016/j.jprd.2020.07.003.

59. Nouri S, Khoong EC, Lyles CR, Karliner L. Addressing equity in telemedicine for chronic disease management during the Covid-19 pandemic. NEJM Catal Innov Care Deliv. 2020. https://doi.org/10.1056/cat.20.0123. Provides key action items to ensure
equitable access to telemedicine including identifying potential disparities, mitigating digital literacy, removing health system created barriers, and advocating for change.

60. Vogels E. Pew Research Center. Digital divide persists even as Americans with lower incomes make gains in tech adoption. https://www.pewresearch.org/fact-tank/2021/06/22/digital-divide-persists-even-as-americans-with-lower-incomes-make-gains-in-tech-adoption/ Accessed December 6th, 2021.

61. Atske S. Pew Research Center. Home broadband adoption, computer ownership vary by race, ethnicity in the U.S. https://www.pewresearch.org/fact-tank/2021/07/16/home-broadband-adoption-computer-ownership-vary-by-race-ethnicity-in-the-u-s/ Accessed December 6th, 2021.

62. Chaudhuri KR, Rukavina K, McConvey V, Antonini A, Lorenzl S, Bhidayasiri R, et al. The impact of COVID-19 on palliative care for people with Parkinson’s and response to future pandemics. Expert Rev Neurother. 2021;21:615–23. https://doi.org/10.1080/14737715.2021.1923480.

63. Zebrak KA, Campione JR. The effect of national family caregiver support program services on caregiver burden. J Appl Gerontol. 2021;40:963–71. https://doi.org/10.1177/0733464819091094.

64. Macchi ZA, Koljack CE, Miyasaki JM, Baloga E, Daeschler M, Sharma S, Dorey ER, Sharma G. A real-world study of wearable sensors in Parkinson’s disease. J Parkinsons Dis. 2020;10:1779–86. https://doi.org/10.3233/JPD-212935.

65. Wiener JM, Anderson WL, Khutatsky G. Are consumer-directed home care beneficiaries satisfied? Evidence from Washington state. Gerontologist. 2007;47:763–74. https://doi.org/10.1093/geront/47.6.763.

66. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20:273–86. https://doi.org/10.1093/biostatistics/kxx069.

67. Institute of Medicine (US). Forum on drug discovery, development, and translation. Transforming clinical research in the United States: challenges and opportunities: workshop summary. Washington (DC): National Academies Press (US); 2010. https://doi.org/10.17226/12900.

68. Vaswani PA, Tropea TF, Dahodwala N. Overcoming barriers to Parkinson disease trial participation: Increasing diversity and novel designs for recruitment and retention. Neurotherapeutics. 2020;17:1724–35. https://doi.org/10.1002/ntu.202000960-0.

69. Prasad S, Kumar H, Bhidayasiri R, Pal PK. Impact of COVID-19 on patient care, training, and research in movement disorders in MDS-AOS region. Mov Disord. 2021;36:2457–8. https://doi.org/10.1002/mds.28802.

70. Shivkumar V, Subramanian T, Agarwal P, Mari Z, Mestre TA, Parkinson Study Group. Uptake of telehealth in Parkinson’s disease clinical care and research during the COVID-19 pandemic. Parkinsonism Relat Disord. 2021;86:97–100. https://doi.org/10.1016/j.parkreldis.2021.03.032. Describes the impact of COVID-19 on movement disorders research operations.

71. U.S. Food and Drug Administration. FDA guidance on conduct of clinical trials of medical products during the COVID-19 public health emergency. August 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency. Accessed December 7th, 2021.

72. European Medicines Agency. Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic. April 2nd, 2021. https://ec.europa.eu/health/sites/default/files/files/medicines/2021-10/guidance-on-clinical-trials-covid19_en.pdf Accessed December 7th, 2021.

73. Tan EK, Albanease A, Chaudhuri K, Lim SY, Oey NE, Shan Chan CH, et al. Adapting to post-COVID19 research in Parkinson’s disease: lessons from a multinational experience. Parkinsonism Relat Disord. 2021;82:146–9. https://doi.org/10.1016/j.parkreldis.2020.10.009.

74. Schneider RB, Myers TL, Rowbotham HM, Luft MK, Amodoe K, Sharma S, et al. A virtual cohort study of individuals at genetic risk for Parkinson’s disease: study protocol and design. J Parkinsons Dis. 2020;10:1195–207. https://doi.org/10.3233/JPD-202019.

75. Schneider RB, Omberg L, Macklin EA, Daeschler M, Bataille L, Anthwal S, et al. Design of a virtual longitudinal observational study in Parkinson’s disease (AT-HOME PD). Ann Clin Transl Neurol. 2021;8:308–20. https://doi.org/10.1002/acn3.51236.

76. Myers TL, Augustine EF, Baloga E, Daeschler M, Cannon P, Rowbotham H, et al. Recruitment for remote decentralized studies in Parkinson’s disease. J Parkinsons Dis. 2021. https://doi.org/10.3233/JPD-212935.

77. Tarolli CG, Andrzejewski K, Zimmerman GA, Bull M, Goldenthal S, Auinger P, et al. Feasibility, reliability, and value of remote video-based trial visits in Parkinson’s disease. J Parkinsons Dis. 2020;10:1779–86. https://doi.org/10.3233/JPD-202163.

78. Mirelman A, Frank MBO, Melamed M, Granovsky L, Nieuwboer A, Rochester L, et al. Detecting sensitive mobility features for Parkinson’s disease stages via machine learning. Mov Disord. 2021;36:2144–55. https://doi.org/10.1002/mds.28631.

79. Adams JLS, Dinesh K, Snyder CW, Xiong M, Tarolli CG, Sharma S, Dorsey ER, Sharma G. A real-world study of wearable sensors in Parkinson’s disease. NPJ Parkinsons Dis. 2021;7:106. https://doi.org/10.1038/s41535-021-00248-w.

80. Lee CY, Kang SJ, Hong SK, Ma HI, Lee U, Kim YJ. A validation study of a smartphone-based finger tapping application for quantitative assessment of bradykinesia in Parkinson’s disease. PLoS One. 2016;11:e0158852. https://doi.org/10.1371/journal.pone.0158852.

81. Gordon MF, Grachev ID, Mazeh I, Dolan Y, Reilmann R, Loupe PS, et al. Quantification of motor function in Huntington disease patients using wearable sensor devices. Digt Biomark. 2019;3:103–15. https://doi.org/10.1159/000502136.

82. Zhan A, Mohan S, Tarolli C, Schneider RB, Adams JL, Sharma S, et al. Using smartphones and machine learning to quantify Parkinson disease severity: the mobile Parkinson disease score. JAMA Neurol. 2018;75:876–80. https://doi.org/10.1001/jamaneurol.2018.0809.

83. Silva de Lima AL, Smits T, Darweesh SKL, Valenti G, Milosevic M, Pijl M, et al. Home-based monitoring of falls using wearable sensors in Parkinson’s disease. Mov Disord. 2020;35:109–15. https://doi.org/10.1002/mds.27830.

84. Lo C, Arora S, Baig F, Lawton MA, El Mouden C, Barber TR, et al. Predicting motor, cognitive & functional impairment in Parkinson’s. Ann Clin Transl Neurol. 2019;6:1498–509. https://doi.org/10.1002/acn3.50853.

85. Mirelman A, Hillel I, Rochester L, Del Din S, Bloem BR, Avanzino L, et al. Tossing and turning in bed: nocturnal movements in Parkinson’s disease. Mov Disord. 2020;35:959–68. https://doi.org/10.1002/mds.28006.

86. Madrid-Navarro CJ, Escamilla-Sevilla F, Mínguez-Castellanos A, Campos M, Ruiz-Abellán F, Madrid JA, et al. Multidimensional circadian monitoring by wearable biosensors in Parkinson’s disease. Front Neurol. 2018;9:157. https://doi.org/10.3389/fneur.2018.00157.

87. Hellman AM, Shah SP, Pawlowski SM, Duda JE, Morley JF. Continuous non-invasive monitoring to detect covert autonomic dysfunction in Parkinson’s disease. Parkinsonism Relat Disord. 2015;21:723–8. https://doi.org/10.1016/j.parkreldis.2015.04.016.
88. Motolese F, Magliozzi A, Puttini F, Rossi M, Capone F, Karlinski K, et al. Parkinson’s disease remote patient monitoring during the COVID-19 lockdown. Front Neurol. 2020;11:567413. https://doi.org/10.3389/fneur.2020.567413.

89. Alberts JL, Koop MM, McGinley MP, Penko AL, Fernandez HH, Shook S, et al. Use of a smartphone to gather Parkinson’s disease neurological vital signs during the COVID-19 pandemic. Parkinsons Dis. 2021;2021:5534282. https://doi.org/10.1155/2021/5534282.

90. Goldsack JC, Izmailova ES, Menetski JP, Hoffmann SC, Groenen PMA, Wagner JA. Remote digital monitoring in clinical trials in the time of COVID-19. Nat Rev Drug Discov. 2020;19:378–9. https://doi.org/10.1038/d41573-020-00094-0.

91. U.S. Food and Drug Administration. Drug Development Tool Letter of Intent Determination DDT COA #000129. https://www.fda.gov/media/139872/download. Accessed December 7th, 2021.

92. U.S. Food and Drug Administration. Drug Development Tool Letter of Intent Determination DDT COA #000142. https://www.fda.gov/media/149517/download Accessed December 7th, 2021.

93. Siddiqi B, Koemeter-Cox A. A Call to action: promoting diversity, equity, and inclusion in parkinson’s research and care. J Parkinsons Dis. 2021;11:905–8. https://doi.org/10.3233/JPD-212593. This editorial highlights the issue of underrepresentation in PD research and areas of focus.

94. Manly JJ, Glymour MM. What the aducanumab approval reveals about Alzheimer disease research. JAMA Neurol. 2021;78:1305–6. https://doi.org/10.1001/jamaneurol.2021.3404.

95. Schneider MG, Swearingen CJ, Shulman LM, Ye J, Baumgarten M, Tilley BC. Minority enrollment in Parkinson’s disease clinical trials. Parkinsonism Relat Disord. 2009;15:258–62. https://doi.org/10.1016/j.parkreldis.2008.06.005.

96. Damron L, Litvan I, Bayram E, Berk S, Siddiqi B, Shill H. Hispanic perspectives on Parkinson’s disease care and research participation. J Alzheimers Dis. 2021;81:809–19. https://doi.org/10.3233/JAD-210231.

97. Stephenson D, Alexander R, Aggarwal V, Badawy R, Bain L, Bhatnagar R, et al. Precompetitive consensus building to facilitate the use of digital health technologies to support Parkinson disease drug development through regulatory science. Digit Biomark. 2020;4:28–49. https://doi.org/10.1159/000512500.

98. Naito A, Wills AM, Tropea TF, Ramirez-Zamora A, Hauser RA, Martino D, et al. Expediting telehealth use in clinical research studies: recommendations for overcoming barriers in North America. NPJ Parkinsons Dis. 2021;7:34. https://doi.org/10.1038/s41531-021-00177-8.

99. Loucks TL, Tyson C, Dorr D, Garovic VD, Hill J, McSwain SD, et al. Clinical research during the COVID-19 pandemic: the role of virtual visits and digital approaches. J Clin Transl Sci. 2021;5:e102. https://doi.org/10.1017/cts.2021.19.

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