The Impact of Upcoming Neurotechnologies on Alzheimer's Disease, Parkinson's Disease, and Spinal Cord Injury

Zeeshan Haq

Abstract:

Neurological conditions are burdensome and have been extremely difficult to treat in the past. These conditions include Alzheimer's Disease, Parkinson's Disease, and spinal cord injury, which cause significant distress for patients and their loved ones. In recent years, advancements in science and biotechnology have allowed for current treatments and future applications for treating these diseases. Fortunately, these upcoming neurotechnologies provide us with the knowledge that there is a brighter future ahead for people who suffer from these conditions. Here, we discuss just some of these future breakthrough technologies, including neuroprosthetics, optogenetics, and pharmacologics, all of which have applications in improving the quality of life for people with Alzheimer's Disease, Parkinson's Disease, and traumatic spinal cord injury.

Introduction:

Neurological and neurodegenerative conditions affect millions of people all over the globe. This includes the 276 million people that suffered from neurological disorders in 2016, leading to 9 million deaths[1]. The total financial burden of this ends up at around 765 billion dollars[2]. This is burdensome, and has an immense impact on patients and families, due to a lack of therapeutics because the nervous system can be very complex, and is something humans are still learning about. Some of the most common of these conditions include Alzheimer's Disease (AD), Parkinson's Disease (PD), and traumatic spinal cord injury (SCI).

Out of these, AD is the most diagnosed in the United States. AD is the chronic degeneration of neurological and mental function, primarily affecting memory, in which death may be an outcome[3]. AD is primarily caused by the deposition of beta amyloids in the brain, but genetic factors can also lead to disease progression[4,5]. Beta amyloids are the byproduct of processes associated with the amyloid precursor protein, or APP. When this protein breaks down, it results in p3 fragments and beta amyloids. Although p3 fragments are nothing to worry about, beta amyloids are the primary cause of AD. In addition to being the primary cause of AD, they can also create neurofibrillary tangles, commonly known as Tau[6]. Tau is a substance that aids in "microtubule binding, axonal transport, and modulation of signaling pathways"[7]. One important factor in the function of tau is phosphorylation. This is a posttranslational modification[8]. Abnormally phosphorylated tau can lead to multiple factors, like the disruption of the sending and receiving of signals between neurons, which can also contribute to memory loss[9–14]. AD is found mostly in people ages 65 and up, specifically around the ages of 84 and 90[3]. As of now, current treatments for AD include therapeutics such as Donepezil and Memantine which both help manage and improve mental function as a whole[15].

Behind AD, PD is the second most diagnosed neurological disorder[16]. PD impacts muscle movement, with symptoms such as muscle rigidity and a resting tremor. PD is caused by the reduction of dopaminergic neurons in the brain, which are important to the brain's cognitive abilities and ability to regulate bodily movement, although to a certain extent, environmental factors like exposure to pesticides, and genetic factors have been linked to the progression of PD[17]. PD is most commonly observed in adults above the age of 85, but can also be found in

younger populations[18]. Possible treatments of PD with today's technology includes physical therapy to help tackle issues with mobility and therapeutics that can increase dopamine levels in the body. This includes drugs such as Levodopa, which is the current therapeutic standard for treating PD[19]. Additionally, Deep Brain Stimulation, or DBS has also been approved by the FDA in the early 2000's to treat PD, by stimulating neurons, which causes an increase in neural activity[20–23].

Finally, another common neurological condition is SCI. SCI is a widespread issue, with 12,500 new cases being added on in North America alone, and 90% of them being caused by traumatic events like automotive accidents, sports, falling, etc[24]. SCI primarily affects men from the ages of 30 to 80, while in women, it is more common in their late teen years and after the age of 70[25]. Frequently, SCI can be the cause of paralysis, which is when a person cannot move or control the movements of a portion of the body. Paralysis is caused by injury to parts of the nervous system, primarily the spinal cord, but sometimes it can be genetic. Current treatments of paralysis caused by traumatic injuries to the spinal cord include physical therapy, but treatments can vary since the condition is relative from person to person.

When taking a look at all of these conditions collectively, the complexity and lack of understanding of the nervous system outlines the lack of effective treatments, compared to treatments for other bodily conditions and diseases. Fortunately, there are many new and upcoming neurotechnologies that aim to effectively treat, and overall, improve daily life for people who have these conditions. Here, we outline the use of neuroprosthetics, optogenetics, and pharmacologicals and their applications as therapeutic interventions to aid the treatment of Alzheimer's Disease, Parkinson's Disease, and traumatic spinal cord injury.

Emerging Technologies

Neuroprosthetics:

Neuroprosthetics are prosthetics devices that interact with the nervous system to rehabilitate functions of the body that may have been impacted by a medical condition or injury. Generally, neuroprosthetics can help restore function to many bodily systems, such as the muscular system, urinary system, and reproductive system with its connection and integrations with the nervous system. But in many cases, neuroprosthetics are used to restore standing and walking motions, as well as hand and arm movements in patients with neurological disorders[26–28]. Out of the current neuroprosthetics available, devices like cochlear implants for hearing impared people and prosthetic devices for people with amputated limbs have been the most successful[29]. One proposition for the use and development of neuroprosthetics is with treating patients with SCI[26–28]. To attempt to restore motor functions and movements, neuroprosthetics use electrodes to stimulate different parts of the nervous system that correspond to restore function to the body. This type of stimulation is called Functional Electrical Stimulation, or FES[30]. FES can be non-invasive, like electrodes placed on the skin, or invasive, like electrodes implanted in the body, both of which trigger nerve stimulation[31,32]. In the brain, the primary motor cortex has been the main area from which motor-related information is extracted from, whether invasively or non-invasively[29]. In a survey conducted by Collinger and collaborators, participants would rather manage FES enabled devices that would improve issues related to movements with the hands, arms, and functions like walking and standing, rather than FES devices that would aid in things like wheelchairs and robotic arms[28]. Future, more ambitious, applications for neuroprosthetics include treatment of conditions like AD and PD[33–36].

Since AD is a disease where memory degradation can lead to further problems down the line, neuroprosthesis systems have been developed “to simultaneously record signals during behavioral tasks and generate with the use of internal neural factors the precise timing of stimulation patterns,” which aim to improve memory function[37]. In regards to PD, low dopamine levels can be countered by a "3D multicellular circuit device in an implantable form" as a way to restore dopamine levels via deep brain stimulation[38].

Neuralink:

One of the most publicized and known neuroprosthetic devices is Neuralink, which was founded by Elon Musk. The company’s main goal is to use this novel neuroprosthetic to “understand and treat brainly disorders,” “preserve and enhance our brain,” and “create a well-aligned future.” Neuralink uses more than 3,000 electrodes implanted in the brain to obtain live data directly from neurons, which should help restore sensory related and motor related functions[33,34,39,40]. This data can then be used accordingly to help with treating whatever neurological condition a patient may have. In PD, for example, the real time data about current brain and neuron activity is extremely useful in treating the disease and building upon current DBS technology[41]. Additionally, paralysis resulting from SCI can be treated by Neuralink; it can use information from a person's brain to control computers and restore motor function in patients. Neuralink can also send information and data back to the brain, so it should be able to allow a person to regain lost senses like touch[42]. Although not tested on humans as of 2022, Neuralink hopes to use its multiple electrodes to stimulate neurons, amplify neurological signals to stimulate more neural activity, and allow for treatments for patients suffering from AD, PD, and Paralysis caused by SCI[41]. Though seeming like science fiction, scientists and engineers are actively trying to make it a safe and intuitive reality for people who suffer from neurodegenerative diseases.

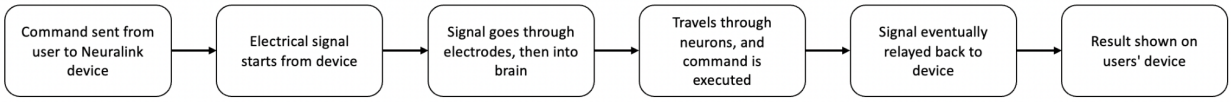

Figure 1: Neuralink’s signal pathway, from the user to the body, then back to the user. In the future, this will help users suffering from neurological diseases continue with their everyday life with simplicity.

Optogenetics and Pharmacologics:

Another stepping stone in the future of neurological care is the advancement of biological and chemical therapeutics. In recent years, biotechnologies like optogenetics, along with new drug concepts such as Aduhelm, or Aducanumab, and Xadago, or Safinamide, have been gaining more attention and been proven to have therapeutic capacity in pre-clinical and clinical trials. These technologies serve differently than neuroprosthetics, as they do not require the use of electrical stimulation or electrodes in their treatment of neurological conditions. Instead, these revolutionary therapeutics allow for the treatment of neurological conditions through expressing opsins in neurons to allow firing upon light activation or the simple ingestion of drugs. Here, we outline the capacity of optogenetics and pharmacologics to treat neurological disorders like Alzheimer’s Disease, Parkinson’s Disease, and spinal cord injury.

Optogenetics:

Optogenetics is a new and upcoming technology that uses a combination of membrane proteins and specific wavelengths of light to stimulate cells in your body[43]. This is made possible by using opsins, which are light sensitive proteins, and when exposed to blue or green light waves, they can conduct neurological activity[44,45] (Figure 2). Because this technology uses an external stimulus to start neurological events, rather than an internal stimulus like your brain, it can circumvent neurological conditions like PD and SCI. For example, because PD results from decreased dopamine levels, optogenetics can instruct the body to produce more dopamine to allow for the return of normal neurological function. This function of Optogenetics has been tested in a mouse model of PD. When these mice are implanted with human stem cells containing halorhodopsin or HALO, a light sensitive inhibitory chloride pump, which is then activated using light, motor ability and dopamine levels are restored[46]. Additionally, in SCI, optogenetics can be used to fire specific neurons to fix respiratory issues, loss of muscular function, loss of reproductive function, loss of control over the urinary system, or even lower body paralysis[43,47,48]. In addition, optogenetics is theorized to help people with AD, although this possibility is still in its early stages[49]. Even though this exciting technology is still in preclinical phases, it remains a hopeful future treatment that will improve the lives of many people all around the world.

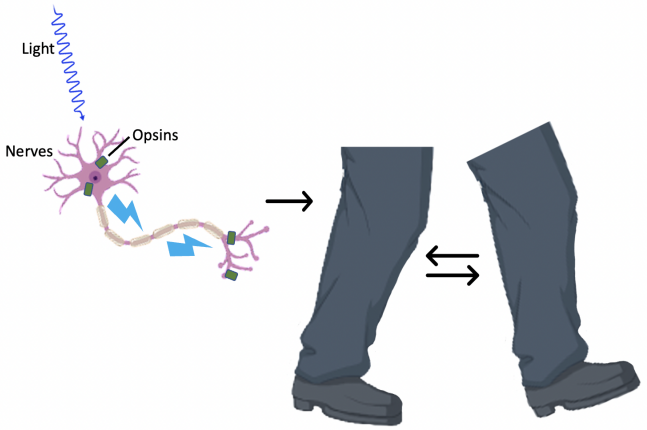

Figure 2: Blue light is shined on neurons from an implanted device. This light activates opsins artificially expressed in neurons to produce a neural signal, leading to movement of paralyzed limbs.

Pharmacologics:

Previously, AD therapeutics have been limited to early preventative treatments. These types of treatments are not very helpful, as patients might not encounter the disease immediately. Treatments like these take years of pretreatment, and it might be too late when treatments start. Currently, the standard for AD treatment include Donepezil and Memantine, which work to improve the function of the brain as a whole. Donepezil works by inhibiting the production of cholinesterase, a neurological inhibitor, and Memanitine serves as a supplement to cholinesterase, and is used as a second line treatment[15,50]. Recently, an FDA approved drug called Aduhelm, or Aducanumab, has been developed to clear plaques from the brain. Aducanumab is a monoclonal antibody drug designed to be given as treatment in the early stages of AD, which targets beta amyloids and clears them from the brain[51]. Monoclonal

antibodies are naturally produced by white blood cells, but can be bioengineered and cloned to treat diseases as a pharmacologic. Monoclonal antibodies have been used in the past to treat conditions like COVID-19, some cancers, and now AD. Aducanumab makes way for more monoclonal antibodies to be made to treat neurodegenerative diseases, like AD. For example, Donanemab is another drug using monoclonal antibody technology that is currently being reviewed by the FDA for approval[52].

The current standard for treating PD is a drug called Levodopa. Levodopa's primary purpose is to serve as a replacement for dopamine, which allows the body to regain its functions that are dopamine-reliant[53]. While Levodopa has been proven to work well in some patients, it often does not take care of all issues and leads to off episodes. However, a new drug called Xadago, or Safinamide, has been developed to allow for treatment during off episodes, or times when a PD patient's current medication isn't working to its full capacity. Safinamide was made to be taken in conjunction with Levodopa, to act as a "booster" during off episodes. Safinamide was tested in two 24 week clinical trials, where the drug was shown to make many improvements to patients' health during off episodes[54]. Safinamide works by inhibiting the production of Monoamine Oxidase B, an enzyme that breaks down dopamine, to reduce symptoms of PD[55–57]. Fortunately, this drug has been approved by the FDA and is just one more of the many pharmaceuticals we are developing to improve the lives of people with PD. Additionally, clinical trials for two monoclonal antibody drugs to treat PD, Cinpanemab and Prasinezumab, were released. These drugs were both in their phase two trials and were 52 weeks long. Unfortunately these two monoclonal antibodies did not prove effective in humans to treat PD[58,59].

Discussion:

In this review, we discuss upcoming neurotechnologies such as neuroprosthetics, optogenetics, and pharmaceuticals and their capacity to treat people suffering from Alzheimer's Disease, Parkinson's Disease, and traumatic spinal cord injury in more effective and reliable ways. Neuroprosthetics provide a more hopeful future for patients with Alzheimer's Disease, Parkinson's Disease, and spinal cord injury by implementing the usage of electrodes to start neural signals in the body. More advanced and futuristic neuroprosthetics, like Neuralink, use artificial intelligence to help enhance the user experience with this device. On the other hand, optogenetics aims to use certain light waves to begin neural signals in the body to help combat Parkinson's Disease and SCI, with goals to improve the quality of life for those living for those with these neurological disorders, with further applications for treating Alzheimer's Disease. Finally, new pharmacologicals like Aducanumab for Alzheimer's Disease and Safinamide for Parkinson's Disease have also been developed and tested to improve the lives of those with these conditions, with even more novel drugs on their way. Although these innovations are very promising, only time will tell which ones will be the most successful for each neurological disorder. In the future, scientific goals include applying these technologies to even more neurological conditions than outlined in this review, including ALS, MS, epilepsy, etc. The future of treating neurological disorders through novel technologies is bright, where patients can still enjoy life without the restraints and suffering of their given disease.

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References:

1. Feigin, V. L. *et al.* Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **18**, 459–480 (2019).
2. Gooch, C. L., Pracht, E. & Borenstein, A. R. The burden of neurological disease in the United States: A summary report and call to action. *Ann. Neurol.* **81**, 479–484 (2017).
3. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. *Alzheimers. Dement.* **15**, 321–387 (2019).
4. Selkoe, D. J. Alzheimer Disease: Mechanistic Understanding Predicts Novel Therapies. *Ann. Intern. Med.* **140**, 627–638 (2004).
5. Querfurth, H. W. & LaFerla, F. M. Alzheimer's disease. *N. Engl. J. Med.* **362**, 329–344 (2010).
6. McLean, C. A. *et al.* Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. *Ann. Neurol.* **46**, 860–866 (1999).
7. Holtzman, D. M. *et al.* Tau: From research to clinical development. *Alzheimers. Dement.* **12**, 1033–1039 (2016).
8. Hu, W. *et al.* Hyperphosphorylation determines both the spread and the morphology of tau pathology. *Alzheimers. Dement.* **12**, 1066–1077 (2016).
9. Hoover, B. R. *et al.* Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. *Neuron* **68**, 1067–1081 (2010).
10. Spires-Jones, T. L. & Hyman, B. T. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron* **82**, 756–771 (2014).
11. Dejanovic, B. *et al.* Changes in the Synaptic Proteome in Tauopathy and Rescue of Tau-Induced Synapse Loss by C1q Antibodies. *Neuron* **100**, 1322–1336.e7 (2018).
12. DeVos, S. L. *et al.* Synaptic Tau Seeding Precedes Tau Pathology in Human Alzheimer's Disease Brain. *Front. Neurosci.* **12**, 267 (2018).
13. Ittner, A. & Ittner, L. M. Dendritic Tau in Alzheimer's Disease. *Neuron* **99**, 13–27 (2018).
14. Gibbons, G. S., Lee, V. M. Y. & Trojanowski, J. Q. Mechanisms of Cell-to-Cell Transmission of Pathological Tau: A Review. *JAMA Neurol.* **76**, 101–108 (2019).
15. Soria Lopez, J. A., González, H. M. & Léger, G. C. Alzheimer's disease. *Handb. Clin. Neurol.* **167**, 231–255 (2019).
16. Dorsey, E. R. *et al.* Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* **68**, 384–386 (2007).
17. Cook Shukla, L. *et al.* Parkinson Disease Overview. in *GeneReviews*® (eds. Adam, M. P. et al.) (University of Washington, Seattle, 2004).
18. Goldman, S. M. *et al.* Concordance for Parkinson's disease in twins: A 20-year update. *Ann. Neurol.* **85**, 600–605 (2019).
19. LeWitt, P. A. Levodopa therapy for Parkinson's disease: Pharmacokinetics and pharmacodynamics. *Mov. Disord.* **30**, 64–72 (2015).
20. Herrington, T. M., Cheng, J. J. & Eskandar, E. N. Mechanisms of deep brain stimulation. *J. Neurophysiol.* **115**, 19–38 (2016).
21. McIntyre, C. C. & Anderson, R. W. Deep brain stimulation mechanisms: the control of network activity via neurochemistry modulation. *J. Neurochem.* **139 Suppl 1**, 338–345 (2016).
22. Farokhniaee, A. & McIntyre, C. C. Theoretical principles of deep brain stimulation induced

synaptic suppression. *Brain Stimul.* **12**, 1402–1409 (2019).
23. Cagnan, H., Denison, T., McIntyre, C. & Brown, P. Publisher Correction: Emerging technologies for improved deep brain stimulation. *Nat. Biotechnol.* **37**, 1237–1237 (2019).
24. Hachem, L. D., Ahuja, C. S. & Fehlings, M. G. Assessment and management of acute spinal cord injury: From point of injury to rehabilitation. *J. Spinal Cord Med.* **40**, 665–675 (2017).
25. Alizadeh, A., Dyck, S. M. & Karimi-Abdolrezaee, S. Traumatic Spinal Cord Injury: An Overview of Pathophysiology, Models and Acute Injury Mechanisms. *Front. Neurol.* **10**, 282 (2019).
26. Anderson, K. D. Targeting recovery: priorities of the spinal cord-injured population. *J. Neurotrauma* **21**, 1371–1383 (2004).
27. Snoek, G. J., IJzerman, M. J., Hermens, H. J., Maxwell, D. & Biering-Sorensen, F. Survey of the needs of patients with spinal cord injury: impact and priority for improvement in hand function in tetraplegics. *Spinal Cord* **42**, 526–532 (2004).
28. Collinger, J. L. *et al.* Functional priorities, assistive technology, and brain-computer interfaces after spinal cord injury. *J. Rehabil. Res. Dev.* **50**, 145–160 (2013).
29. Kansaku, K. Neuroprosthetics in systems neuroscience and medicine. *Sci. Rep.* **11**, 1–3 (2021).
30. Brown-Triolo, D. L., Roach, M. J., Nelson, K. & Triolo, R. J. Consumer perspectives on mobility: implications for neuroprosthesis design. *J. Rehabil. Res. Dev.* **39**, 659–669 (2002).
31. Davis, J. A., Jr *et al.* Surgical technique for installing an eight-channel neuroprosthesis for standing. *Clin. Orthop. Relat. Res.* 237–252 (2001).
32. Fisher, L. E., Tyler, D. J., Anderson, J. S. & Triolo, R. J. Chronic stability and selectivity of four-contact spiral nerve-cuff electrodes in stimulating the human femoral nerve. *J. Neural Eng.* **6**, 046010 (2009).
33. Dadia, T. & Greenbaum, D. Neuralink: The Ethical ‘Rithmatic of Reading and Writing to the Brain. *AJOB Neurosci.* **10**, 187–189 (2019).
34. Fourneret, É. The Hybridization of the Human with Brain Implants: The Neuralink Project. *Camb. Q. Healthc. Ethics* **29**, 668–672 (2020).
35. Pisarchik, A. N., Maksimenko, V. A. & Hramov, A. E. From Novel Technology to Novel Applications: Comment on ‘An Integrated Brain-Machine Interface Platform With Thousands of Channels’ by Elon Musk and Neuralink. *J. Med. Internet Res.* **21**, e16356 (2019).
36. Hennig, M. H., Hurwitz, C. & Sorbaro, M. Scaling Spike Detection and Sorting for Next-Generation Electrophysiology. *Adv Neurobiol* **22**, 171–184 (2019).
37. Cutsuridis, V. Memory Prosthesis: Is It Time for a Deep Neuromimetic Computing Approach? *Front. Neurosci.* **13**, 667 (2019).
38. Prox, J. *et al.* Toward living neuroprosthetics: developing a biological brain pacemaker as a living neuromodulatory implant for improving parkinsonian symptoms. *J. Neural Eng.* **18**, (2021).
39. Kulshreshth, A., Anand, A. & Lakanpal, A. Neuralink- An Elon Musk Start-up Achieve symbiosis with Artificial Intelligence. in *2019 International Conference on Computing, Communication, and Intelligent Systems (ICCCIS)* 105–109 (2019).
40. Musk, E. & Neuralink. An Integrated Brain-Machine Interface Platform With Thousands of Channels. *J. Med. Internet Res.* **21**, e16194 (2019).
41. Fiani, B., Reardon, T., Ayres, B., Cline, D. & Sitto, S. R. An Examination of Prospective Uses and Future Directions of Neuralink: The Brain-Machine Interface. *Cureus* **13**, e14192

(2021).
42. Balasubramanian, S. Elon Musk's Neuralink Is Attempting To Make Brain-Machine Interfaces To Help Individuals With Paralysis. *Forbes Magazine* (2020).
43. Ahmad, A., Ashraf, S. & Komai, S. Optogenetics applications for treating spinal cord injury. *Asian Spine J.* **9**, 299–305 (2015).
44. Boyden, E. S. A history of optogenetics: the development of tools for controlling brain circuits with light. *F1000 Biol. Rep.* **3**, 11 (2011).
45. Adamantidis, A. R., Zhang, F., de Lecea, L. & Deisseroth, K. Optogenetics: opsins and optical interfaces in neuroscience. *Cold Spring Harb. Protoc.* **2014**, 815–822 (2014).
46. Steinbeck, J. A. *et al.* Optogenetics enables functional analysis of human embryonic stem cell-derived grafts in a Parkinson's disease model. *Nat. Biotechnol.* **33**, 204–209 (2015).
47. Zimmer, M. B., Nantwi, K. & Goshgarian, H. G. Effect of spinal cord injury on the respiratory system: basic research and current clinical treatment options. *J. Spinal Cord Med.* **30**, 319–330 (2007).
48. Onders, R. P. *et al.* Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients. *Surg. Endosc.* **23**, 1433–1440 (2009).
49. Wang, K.-W., Ye, X.-L., Huang, T., Yang, X.-F. & Zou, L.-Y. Optogenetics-induced activation of glutamate receptors improves memory function in mice with Alzheimer's disease. *Neural Regeneration Res.* **14**, 2147–2155 (2019).
50. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. *J. Am. Geriatr. Soc.* **63**, 2227–2246 (2015).
51. Ferrero, J. *et al.* First-in-human, double-blind, placebo-controlled, single-dose escalation study of aducanumab (BIIB037) in mild-to-moderate Alzheimer's disease. *Alzheimers. Dement.* **2**, 169–176 (2016).
52. Mintun, M. A. *et al.* Donanemab in Early Alzheimer's Disease. *N. Engl. J. Med.* **384**, 1691–1704 (2021).
53. Koller, W. C. & Rueda, M. G. Mechanism of action of dopaminergic agents in Parkinson's disease. *Neurology* **50**, S11–S14 (1998).
54. Cruz, M. P. Xadago (Safinamide): A Monoamine Oxidase B Inhibitor for the Adjunct Treatment of Motor Symptoms in Parkinson's Disease. *P T* **42**, 622–637 (2017).
55. Fénelon, G., Mahieux, F., Huon, R. & Ziégler, M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain* **123 (Pt 4)**, 733–745 (2000).
56. Schrag, A., Ben-Shlomo, Y. & Quinn, N. How common are complications of Parkinson's disease? *J. Neurol.* **249**, 419–423 (2002).
57. Goetz, C. G., Fan, W., Leurgans, S., Bernard, B. & Stebbins, G. T. The Malignant Course of 'Benign Hallucinations' in Parkinson Disease. *Arch. Neurol.* **63**, 713–716 (2006).
58. Lang, A. E. *et al.* Trial of Cinpanemab in Early Parkinson's Disease. *N. Engl. J. Med.* **387**, 408–420 (2022).
59. Pagano, G. *et al.* Trial of Prasinezumab in Early-Stage Parkinson's Disease. *N. Engl. J. Med.* **387**, 421–432 (2022).