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Neuromodulation Technologies for the Treatment of Alzheimer Disease

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Key Messages

- There are not very many effective treatment options for Alzheimer disease most of the options have side effects and temporarily reduce symptoms rather than delay disease progression. Effective treatments with minimal side effects that prevent and reduce the severity of Alzheimer disease are needed. Neuromodulation techniques have recently emerged for the treatment of Alzheimer disease, with the hope of filling some of these treatment gaps.
- Two invasive and 8 noninvasive techniques are described in this Horizon Scan, some with more published evidence than others. Deep brain stimulation, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and transcranial alternating current stimulation have more published studies involving patients with Alzheimer disease. Technologies at an earlier stage of development and with fewer studies providing an evidence base include vagus nerve stimulation, ultrasound stimulation, electromagnetic stimulation, photobiomodulation, infrared stimulation, and auditory stimulation.
- The evidence regarding neuromodulation techniques is mostly promising; however, most studies are preliminary or include fewer than 50 participants. Given the heterogeneous nature of Alzheimer disease and the variety of methods in which the different neuromodulation technologies can be used, more research is needed to determine the effectiveness and relative effectiveness of neuromodulation techniques and devices.
- Limitations in the research include limited evidence on the long-term effects and cost-effectiveness of the techniques in the treatment of Alzheimer disease, as well as the clinical significance of the results in the published studies thus far.
- Despite the limited evidence, the results emerging from the literature are hopeful for many people living with Alzheimer disease. Importantly, the lack of reported serious side effects is a hopeful start for many who currently experience difficulties with pharmaceuticals. Given the heterogeneous nature of Alzheimer disease, the increased variety in treatment options also offers hope in potentially finding more effective treatments for individuals living with the debilitating disease.

Purpose

The purpose of this Horizon Scan is to present health care stakeholders in Canada with an overview of information related to emerging neuromodulation techniques for the treatment of Alzheimer disease, a description of some of the published evidence, and a summary of some considerations related to operational considerations should the emerging evidence demonstrate value. This report is not a systematic review and does not involve critical appraisal or include a detailed summary of study findings. Rather, it presents an overview of the technologies and available evidence. It is not intended to provide recommendations.

Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, Scopus, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major

international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concepts were neuromodulation and Alzheimer disease. No filters were applied to limit the retrieval by study type. Comments, newspaper articles, editorials, and letters were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2016 and June 16, 2021. Internet links were provided, where available.

Regular alerts updated the search until project completion; only citations retrieved before August 20th, 2021 were incorporated into the report.

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was any neuromodulation technique and for the treatment of Alzheimer disease. Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

Peer Review

A draft version of this bulletin was reviewed by 1 clinical expert, with expertise in geriatrics, health policy, and health care delivery.

Background and Current Practice

Alzheimer disease (AD) is the most common form of dementia worldwide, representing more than 60% of dementia diagnoses.[1-3] Although the disease primarily affects older adults (i.e., those 65 and older), when symptoms appear before 65 the disease is referred to as young- or early-onset AD. Young-onset AD can start occurring as early as 30 and represents an estimated 2% to 8% of AD cases in Canada.[4] AD has a mean life expectancy of approximately 7 years after diagnosis,[5] creating a large burden on families, caregivers, and the public health system.[2,3,6] Not only is AD a burden on individuals and families, but it is a costly disease. Worldwide spending on dementia care was estimated to be US$422 billion in 2009 and is projected to increase.[7] In 2016, it was estimated that more than $10 billion was spent annually to bring care to people in Canada living with dementia and AD, and this was also projected to increase.[1] Although AD pathogenesis is not completely understood, it is generally agreed that abnormalities in memory circuits are involved.[8] The disease is characterized by widespread accumulation of amyloid plaques and intraneuronal neurofibrillary tangles in the brain,[2] reducing the capacity of neural circuits to properly function, leading to memory dysfunction and cognitive impairments.[9] Specifically, hippocampal atrophy and cholinergic neuronal loss in the nucleus basalis of Meynert have been observed in many people with AD.[10] The extent of neuronal damage in different regions of the brain varies, making treatment difficult. Symptoms that present in patients with AD include but are not limited to progressive memory loss, difficulty with communication, decline in functioning associated with completing activities of daily living, and neuropsychiatric symptoms such as hallucinations, mood changes, and apathy agitation.[3,6] As the condition progresses, the symptoms increase and the need for supervision increases, and this in turn increases the burden on family

members and caregivers.[11] Not all people exhibit the same symptoms or to the same degree, making the disease heterogenous in nature.

Current treatment for AD involves the use of pharmacological and psychosocial treatments. The 2 main categories of medications given for AD are cholinesterase inhibitors and glutamate antagonists, which all may be accompanied by adverse effects.[6] Furthermore, none of the pharmacological or psychosocial therapies available successfully slow or reverse the progression of AD.[6,10] Pharmacological treatments alleviate symptoms temporarily and have not been effective for all people with AD, leaving many people without effective treatment and hoping for other options.[12] This has led to the investigation of different neuromodulation techniques for the treatment of AD, many of which are currently being used for other neurologic and psychiatric disorders. Given the heterogeneity of the disease, the lack of effective treatments, and the number of people in Canada living with AD, exploring the potential use of neuromodulation techniques has become an evolving field of interest to researchers, caregivers, and patients with AD.

Who Might Benefit?

The devices and technologies described in this report could result in benefits for any person who experiences AD. Current recommendations for the treatment of AD are limited to pharmacological and psychosocial interventions, which are not effective for all people and only temporarily reduce the burden of AD. And, as previously stated, more treatment options may help reduce the burden of the disease on those living with the disease, their families, and caregivers.

In Canada, there are gaps in the data regarding AD statistics and information is often reported on dementia overall rather than AD and dementia separately. The Canadian Study of Health and Aging conducted between 1991 and 2001 is often referenced to demonstrate that the incidence of new cases of AD is rising, but more recent data on the incidence of AD has not been reported.[13] Some studies have reported that international incidence rates (the rate of new cases within a population) of AD and other dementias may be decreasing. It is thought that this may be due to improvements in the prevention of cerebrovascular diseases, but this has not been confirmed.[13] While the exact incidence of AD in Canada is not known, Canada has an aging population and the risk of developing a chronic disease such as AD increases with age.[14] In terms of prevalence (the number of active cases within a population), estimates vary. In 2012, the Alzheimer Society of Canada reported that 747,000 people in Canada were living with AD, whereas in 2010 it was estimated that 500,000 people in Canada were living with the disease.[11] In 2019, 154,300 people in Canada aged 65 years or older were living with AD — 93,300 of which were women and 61,000 were men.[15] Regardless of the exact number, a 2016 report found that for those aged 45 to 65 years living with dementia in Canada, 99% were unemployed, citing the disease as the reason and demonstrating the impact that dementia has on everyday life.[11] People living with AD often require a caregiver. Most often, the caregiver is a family member, with 46% of people living with dementia reporting their spouse as their caregiver and 44% citing an adult child providing care. In both cases, care is almost always provided on a daily basis, increasing the burden of the disease on families as a whole.[11] The combination of AD being an age-related neurodegenerative disorder, the prevalence of the disease on the rise, and Canada's aging population makes finding successful treatments for AD of vital importance.[16]

The Technologies

This report describes emerging neuromodulation technologies for the treatment of AD. These include 2 invasive techniques and 8 noninvasive stimulation techniques for the treatment of any stage of AD. The most common methods of evaluating clinical outcomes within the studies included, but were not limited to the Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale (ADAS), the Montreal Cognitive Assessment (MoCA), and the Clinical Dementia Rating (CDR) scale. For the scales used, a clinically significant change in cognition for patients with AD has been identified as a 1- to 3-point change in score on the MMSE,[17] a 4-point change in score on the ADAS,[18] or a 1- to 2-point change in score on the CDR scale.[17] Although it was not identified what a clinically relevant change on the MoCA is for people with AD, the scale has been validated within the population, detecting 100% of people with mild AD.[19] If studies did not specify whether a finding was clinically significant but the results aligned with the described parameters, this was identified in the text.

Invasive Stimulation Techniques

Deep Brain Stimulation

The Deep Brain Stimulation (DBS) technique involves the surgical implantation of an electrode to a nucleus or fibre tract in the brain, as well as the embedment of a pulse generator underneath the skin on the chest or abdomen.[8,16] Clinical trials for DBS in AD treatment first started in 1984; however, due to varying electrical current intensities, frequencies of stimulation, and locations for implantation of the electrode, results have been inconclusive.[8] The main target areas in human clinical studies for implementation are the nucleus basalis of Meynert, the fornix, and the entorhinal cortex-hippocampal network,[16] with stimulation frequency ranging from 10 Hz to 100 Hz.[16] Because of the invasive nature of DBS, it is suggested that it can more directly target specific neural circuits compared to noninvasive techniques.[8] Currently, DBS technology is authorized for the treatment of essential tremor and advanced Parkinson disease in Canada, as well as epilepsy and obsessive-compulsive disorder in other regions.[20]

The authors of 1 systematic review[16] concluded that DBS is a promising intervention for people with AD after finding that 14 out of 16 trials showed a therapeutic effect of the technique, with mean ADAS-Cog score changes ranging from 0.7 to 6 points and the mean MMSE score changes ranging from 0.6 to 4 points across the 16 trials. The authors further concluded that optimal DBS frequency is unclear. The study also found inconclusive results from human clinical trials regarding whether DBS implementation is more successful in younger or elderly patients, but did report preliminary findings suggesting that unilateral DBS may be safer than bilateral DBS.[16] Overall, the study concluded that individual differences need to be further examined given the diversity of DBS parameters.[16] Other systematic reviews investigating stimulation of the fornix[2,16] and the nucleus basalis of Meynert[2] with DBS also report promising but inconclusive findings, concluding that DBS appears to be a feasible and safe intervention for patients with AD, but that human research is limited to preliminary results and that different stimulation parameters need to be further investigated because of the heterogenous symptoms associated with AD.[2,12] While preliminary efficacy and safety studies have had positive findings pointing to the potential effectiveness for the treatment of AD, most studies have small sample sizes (fewer than 50 people) consisting of participants with mild AD, with follow-up shortly after DBS and with a lack of long-term evidence of cognitive benefits.[2]

After the promising safety results from 1 of the most highly referenced DBS-fornix trials for the treatment of AD — the phase IIb, randomized, double-blind ADvance Study[21] — Functional Neuromodulation's DBS system was approved for the treatment of AD in Europe. At the time of publication, the same researchers are conducting ADvance II Study, with 210 patients compared to 42 in the original pilot study, to provide the data required to seek approval for their device Vercise DBS System in the US.[20,22]

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) can be completed as an invasive technique, where a small pulse generator is surgically implanted in the left thoracic region of the spine, as well as non-invasively where the stimulator is placed on the ear.[23] Compared to other stimulation techniques, where a region of the brain is stimulated directly, VNS indirectly modulates different regions of the brain along its pathway such as the brain stem, thalamus, and the limbic system.[23,24] The vagus nerve is part of the regulatory regions for breathing, heart rate and digestion, pain, memory, and mood.[25] Although VNS can have an impact on memory consolidation and performance, there is uncertainty as to how symptoms are improved.[23,24] Previously, VNS has been used as a treatment option for conditions such as treatment-resistant epilepsy, treatment-resistant depression, migraines, schizophrenia, and anxiety disorders, leading to the exploration of its use in other psychiatric conditions such as AD.[23,24]

Two different systematic reviews — 1 completed in 2017[23] and 1 in 2020[24] — and 1 review from 2018[7] found the same 2 studies investigating the use of VNS as a treatment option for AD in humans. Both of the studies were non-randomized pilot studies without a control group and both used the invasive VNS technique.[23,24] The first study involved 10 participants with AD, who received 20 Hz pulse treatment and were followed for 3 months.[7] After the first 3 months, 7 of the patients showed a median improvement of 3 points on the ADAS-Cog score and 9 showed a median improvement of 1.5 points on the MMSE,[23] of which the reported change on the MMSE has been referred to as a clinically relevant change in scores.[18,19] Due to the positive cognitive effects seen, the trial was extended to 6 months, where the effects were sustained with minimal adverse events reported.[7] After the positive findings, the researchers recruited 7 more patients with AD to conduct the second study and found similar results after 1 year of follow-up.[7]

Noninvasive Stimulation Techniques

Transcranial Magnetic Stimulation

Repetitive Transcranial Magnetic Stimulation

Repetitive Transcranial Magnetic Stimulation (rTMS) is a noninvasive neuromodulation technique whereby a device containing a coil is placed on the scalp, releasing electrical currents and creating a magnetic field as the currents radiate and return to the conductor.[26] When the current is strong enough, it can depolarize neurons in a targeted area 2 cm to 3 cm beneath the surface, indirectly affecting regions connected to these sites and potentially regulating cortical function.[6,26] Although a specific protocol has not been identified for rTMS for AD, most studies have investigated placement over the front of the head — specifically, the dorsolateral prefrontal cortex — based on the protocol for multiple depressive disorder, with high, theta, or low-frequencies.[26,27] The most commonly used clinical protocols also involve an application for 20 to 40 minutes over a period of 2 to 5 weeks.[27]

For short-term cognitive effects, high frequency rTMS has demonstrated positive results, although whether the results are clinically meaningful is uncertain. A meta-analysis of

randomized controlled trials[6] and a systematic review with meta-analysis[27] reported that rTMS for AD resulted in statistically significantly improved short-term cognitive function of participants (standard mean difference [SMD] for MMSE and ADAS-Cog = 0.42; 95% CI, 0.18 to 0.67, P = 0.0006;[6] mean pre-post MMSE change 1.08; 95% CI, 0.35 to 1.80),[27] with high frequency rTMS rated as the best short-term intervention for general cognitive function when compared to other electrical stimulation interventions. Furthermore, statistically significant effects on cognitive function were seen when multiple sites (SMD = 0.47; 95% CI, 0.14 to 0.79; P = 0.005) were stimulated compared to single-site stimulation (SMD = 0.24; 95% CI, −0.45 to 0.92; P = 0.50), with cognitive scores improving as patients received longer-term treatment (more than 10 sessions) and higher frequency (20 Hz versus 10 Hz or 1 Hz).[6] Notably, it was reported that rTMS improved the cognitive function of patients with mild to moderate AD when followed for up to 3 months (SMD = 0.45; 95% CI, 0.20 to 0.70; P = 0.0004), with this effect not seen in the patients with severe AD (SMD = 0.01; 95% CI, −0.95 to 0.97; P = 0.42).[6]

Not only has rTMS been compared to other neuromodulation technologies, but a recent cohort study evaluated the long-term effects of rTMS in conjunction with cognitive training compared to pharmacological interventions.[28] The authors found that compared to participants who were given acetylcholinesterase inhibitors, participants who received rTMS and cognitive training showed a significantly slower rate of cognitive decline over 3 years (MMSE = −0.93, P = 0.01; CDR = 0.53, P = 0.03).[28] It is important to highlight that although many protocols involve cognitive training, the training has not been found to provide any additional positive effects and similar results have been demonstrated when rTMS is delivered alone.[27]

Several rTMS devices have been developed, 1 of which is NeuroAD. A randomized controlled trial evaluated the efficacy of 30 sessions of the rTMS device NeuroAD in conjunction with cognitive training in patients with mild to moderate AD.[29] The NeuroAD device, developed by Israel-based Neuronix, targes multiple stimulation sites at a frequency of 10 Hz. Throughout the trial, all adverse events were mild, with most resolving within 1 day. The authors reported that at 12 weeks, the group receiving the NeuroAD device had sustained cognitive improvement (mean change in ADAS-Cog score of −2.11) compared to the control group, which had improved in cognition only to return to baseline by week 12.[29] Although, in another trial it was reported that after 6 months, sustained cognitive improvement after using the NeuroAD device was no longer seen in all patients.[30] Currently, the NeuroAD device is approved for use in Europe, Australia, and the UK but was rejected for clearance by the FDA in March of 2019.[31]

Electrical Stimulation

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is a noninvasive electrical neuromodulation technique. A weak current is passed between electrodes in a device placed on the head, leading to the activation of neurons and the stimulation of the brain.[32] The exact mechanism of tDCS is still unclear, but it is generally agreed that the current can adapt a threshold potential, thereby altering responses within neurons.[32] Similar to other neuromodulation techniques, a precise protocol for AD has not been determined. For example, the tDCS technique can be applied in an anodal or cathodal manner at either a high or low frequency and over any region of the brain. This variability in protocols has led to inconsistent conclusions regarding the applicability of tDCS for the treatment of AD. Previously, tDCS has been used to treat symptoms of stroke, epilepsy, Parkinson disease, and depression.[33]

Most of the literature on tDCS for people with AD is inconclusive, with many individual studies reporting positive results that are limited by small sample sizes. For example, positive results have been reported on the impact of tDCS on verbal fluency when the electrode is placed over the right dorsolateral prefrontal cortex (n = 40),[34] on stabilizing cognition when applied daily over the left dorsolateral prefrontal cortex (n = 18),[35] and on overall cognition when placed over the left and right temporoparietal region (n = 46).[36] Notably, these 3 studies all compared to sham procedure, making comparisons between study protocols difficult.

Overall, consensus is lacking on the most effective protocol for the application of tDCS and the overall effectiveness of the technique. Furthermore, from the studies identified, whether the results thus far are clinically meaningful is uncertain. A meta-analysis of trials from 2019 investigating tDCS in participants with mild AD compared study protocols and found that cognitive scores measured using word recognition memory, visual recognition memory, MMSE, and the Face-Name Associative Memory Task were statistically significantly improved in patients with AD after a single session but not after repeated sessions (SMD = 0.84; 95% CI, 0.30 to 1.37; P = 0.002 versus SMD = 0.19; 95% CI, −0.14 to 0.52; P = 0.26).[33] Subgroup analyses also showed that lower versus higher frequency and stimulation over the temporal lobe versus the left dorsolateral prefrontal cortex led to a statistically significant improvement in cognition. Although the results trend toward tDCS being effective, the sample size was small and results should be interpreted with caution.[33] On the other hand, a systematic review from 2021 investigating the effect of tDCS in patients with AD found that studies with similar protocols reported conflicting results whether tDCS was an effective therapeutic tool for general cognitive function and working memory, and concluded that the technique was not effective for memory, language and verbal fluency, and executive functions.[32] Although, when compared to anodal tDCS and rTMS interventions, a systematic review with meta-analyses from 2021 did find that cathodal tDCS technology resulted in the greatest long-lasting effects at 1-month follow-up for patients with AD, with statistically significant effects seen for general cognitive functions and working memory.[27]

Transcranial Alternating Current Stimulation

There are fewer published studies evaluating transcranial alternating current stimulation (tACS) for the treatment of AD compared to the tDCS technique. Similar to tDCS, electrodes can be placed over various regions of the brain, which oscillate a current at a particular frequency to interact with ongoing neuronal activity with the intent of having an effect on cognition changes.[37] The main difference between the 2 techniques is that, in tACS, the current alternates starting at the different nodes.

The evidence regarding tACS for AD is emerging, as most research has been conducted on animals or healthy subjects. Pilot studies have been conducted in older adults and those presenting with cognitive impairment with promising results. One pilot study examined whether 30-minute daily sessions of 40 Hz in conjunction with brain exercises for 4 weeks would improve cognitive function in adults 63 to 77 years of age with mild cognitive impairment.[38] It was reported that the patients who received tACS maintained memory improvement at the 1-month follow-up, whereas those who did not receive tACS did not.[38] One randomized controlled trial using tACS for participants with AD was in the recruitment phase as of July 2021, investigating the impact of 40 Hz tACS in patients with mild AD.[37] The authors are investigating the wearable NEXALIN ADI device involving 3 electrodes to target the bilateral frontal and temporal lobes and the patients will receive 30 1-hour sessions over 3 weeks.[37]

A recent case series investigated the possibility of a home-based 40 Hz tACS system that could be safely administered by caregivers for people with AD.[39] After completing a pilot laboratory-based study, the authors reported that 10 or 20 stimulations were not enough to produce sustained cognitive effect and were looking for a method to make tACS more accessible for patients and caregivers. In their study, the spouses of 2 79-year-old men with established dementia were taught how to administer the tACS system, which consisted of a cap containing electrodes. After 14 weeks, both of the participants exhibited improved cognitive effects, an overall 10- and 15-point improvement on the MoCA, with a change from 5 to 11 on the Memory Index score, demonstrating that a remotely supervised, home-based tACS system is feasible and could be a potentially effective intervention.[39]

Ultrasound Stimulation

Ultrasound stimulation is a noninvasive approach whereby targeted and accurate stimulation of different regions in the brain can be accomplished.[40] Given the ability to be accurate with the technology, ultrasound technology is generally referred to as focused ultrasound when it is targeting a precise brain region.[25] Ultrasound stimulation can be of high or low intensity, with low intensity being the level used to adapt neural circuits with pulsed or continuous sonication.[25,41] Regarding the target of the technology, transcranial pulse stimulation targets both shallow and deep brain regions or the technology can be used to impact the permeability of the blood brain barrier.[40-42] Low-intensity-focused ultrasound has shown positive results in the treatment of epilepsy and mood disorders, leading to the exploration in AD.[25]

In transcranial pulse stimulation, short ultrasound pulses are believed to alter cell ion channels, thereby impacting neurotransmitter levels.[40] A recent pilot study of 35 patients with probable AD found that this technique improved memory performance when evaluated with the Consortium to Establish a Registry for Alzheimer's Disease scoring system, while reporting no major side effects — a promising preliminary result for the technique.[43]

The other target for ultrasound stimulation, blood brain barrier (BBB) opening, has more published studies in humans thus far and is a reversible process modulated by the intensity of the ultrasound frequency.[40] By altering the permeability of the BBB, neural activity can be temporarily altered.[44] Additionally, altering the permeability of the BBB has shown to be a promising approach to improve drug delivery, suggesting a potential for this technology to be used in conjunction with pharmaceuticals.[41] It is thought that when there is an imbalance between the production and the clearance of the beta-amyloid peptide, which happens via the BBB, progressive dysfunction of the brain can occur.[40] In a phase I safety study, it was reported that although the technique was deemed safe, AD-specific outcome measures were unchanged before and after the procedure in 5 patients with AD.[42]

Currently, there are a few devices that use ultrasound technology and are being investigated for their use in patients with AD. The SonoCloud device was developed by Carthera in France and is surgically implanted under the skull to ensure the bone does not impact the quality of the low-intensity ultrasound waves.[40] The device uses the concept of opening the BBB and has shown promising results in patients with gliomas, with the BOREAL1 trial currently assessing the technology for use in patients with mild AD.[40] The Korean company Neurosona has also created a low-intensity-focused ultrasound device that has undergone pilot studies for AD.[45] It is not clear, however, when either of the devices will seek FDA approval or Health Canada authorization.

Electromagnetic Treatment

Transcranial electromagnetic treatment (TEMT) is similar to the previously described TMS treatment. Unlike TMS treatment, both magnetic and electric waves are emitted from the source, which disperse within the brain and do not return.[40] Although the mechanism of effect of TEMT is not entirely understood, it is suggested that the magnetic and electric fields emitted by the treatment devices have the capability of modifying cortical activity.[40]

In a clinical trial from 2019, 8 participants with mild or moderate AD were administered TEMT in their homes for 2 months using the MemorEM device.[46] The MemorEM device, developed by NeuroEM Therapeutics, is a wearable head device that transmits waves at 915 MHz and 1.6 W/kg average power.[47] On October 28, 2020 the device was given a Breakthrough Device designation by the FDA — a reflection of the promising results seen in the device's ability to reverse memory loss.[48] The device can be worn and can deliver treatment as users complete most tasks they would regularly; it was worn for 1 hour each day during the trial.[46] After the trial, no discomfort or physiologic changes were reported by any of the participants, while at the same time, clinically important (ADAS-Cog scores improved by 4.1 points) and statistically significant improvements were seen in cognitive measures. Notably, participants were motivated to continue treatment, leading to a 4-month extension of the trial, where stable or improved cognitive functions were reported.[46] Because of the success of the pilot study, the Gen2 MemorEM device is to go through a 12-month clinical trial, anticipated to start mid-2022, to provide evidence for seeking FDA approval for its use in the treatment of AD; it is hoped it will be commercialized by 2024.[47]

Photobiomodulation Stimulation

Photobiomodulation (PBM) is a form of electromagnetic stimulation involving the use of laser technology that emits photons stimulating the mitochondria in different regions of the brain.[40] Light used in PBM is in the range of visible red (620 nm to 750 nm) to near-infrared (750 nm to 1,400 nm), stimulating the mitochondria and thereby reducing oxidative stress, preventing neurodegeneration, and producing energy, which is required for nerve cells to function.[40,41,49] So far, most of the research involving PBM has been for the treatment of stroke and traumatic brain injury, but the results for those conditions has led to interest in the use of the technology for patients with AD.[41]

A 2021 review described 2 studies completed with patients with AD using a wearable intranasal PBM device for 12 weeks, a case series following 5 participants with dementia or AD with weekly transcranial PBM plus daily intranasal PBM,[50] and a randomized controlled trial with 8 participants.[40] Both of the studies reported clinically meaningful changes in cognitive measures, a mean + 2.60-point change on the MMSE and mean –6.73-point change on the ADAS-Cog from the case series.[50] There was also an improvement in the ADAS-Cog scores from the randomized controlled trial,[40] although the case series did note that, after the cessation of treatment, the improvements did not remain.[41] Additionally, a randomized controlled trial from 2021 involved 60 participants with anemia and AD and found that the combined intervention of moderate-intensity aerobic exercise with low-level intranasal PBM showed a statistically significant improvement in MoCA scores among the group receiving PBM for 12 weeks versus placebo, demonstrating that combined aerobic activity and PBM may be a safe and effective way of improving cognition among people with AD who also have anemia.[51]

Transcranial Infrared Brain Stimulation

Transcranial infrared brain stimulation (TIBS) is a more specific form of photobiomodulation using solely infrared wavelength of light.[49] Infrared light is of interest for the treatment of AD because of its demonstrated ability to influence functions of the frontal cortex, thereby improving attention, memory, and mood in humans — 3 things commonly affected in people living with the disease.[52] Being a newer technique, the ideal parameters such as the beam diameter, wavelength, power density, and electromagnetic energy density, have not been determined. A review in 2020 found evidence of potentially successful parameters to improving cognitive function in 2 studies involving healthy volunteers, suggesting that a wavelength of 1,064 nm may result in positive outcomes, leading to the ongoing investigation of the same parameters within patients with mild cognitive impairment.[49] Although studies have not been completed involving patients with AD, evidence of the ability of TIBS to alter mitochondria in synapses, axons, and other major sites disrupted in AD has led to interest in TIBS as a possible treatment option for AD.[49]

Auditory Stimulation

Based on the concept that memory consolidation occurs in deep, slow sleep and that sleep deprivation may impact new memory consolidation, some researchers have begun investigating auditory stimulation for the treatment of AD. Thus far, acoustic brain stimulation using pink noise while a person sleeps has demonstrated promising results regarding memory consolidation in healthy volunteers.[40] Building off these findings in healthy volunteers, a study is being conducted in France to assess proof of concept of a device using auditory brain stimulation to impact memory capacity among a group of participants with AD and as of August 2021 has not started recruiting.[53]

Cognito Therapeutics in the US is also investigating the concept of combining auditory stimulation with visual stimulation at the same time, using gamma oscillations, which have been shown to facilitate memory activity.[40,54] Its device, which received a Breakthrough Device designation on January 12, 2021, combines 40 Hz of light and sound to stimulate gamma frequency in the brain.[54] Although the device has shown promising results in animals, results from human studies have yet to be published.

Availability

Currently, none of the mentioned techniques or devices have been authorized for use in Canada for AD. In February 2021, Ontario Health recommended publicly funding rTMS for people with treatment-resistant depression; however, no recommendations have been made for the use of neuromodulation techniques for the treatment of AD.[55] As of the publication of this document, there are multiple clinical trials being completed in Canada for some of the techniques, suggesting potential approval down the line if they are found effective:

- A trial using DBS technology for the treatment of AD is being completed in Ontario, with a targeted completion in 2023.[56]
- Two different trials in the recruitment phase in Ontario are investigating the use of tDCS — 1 looking at treating neuropsychiatric or behavioural and psychiatric symptoms of dementia[57] and the other investigating cognitive outcomes in mild cognitive impairment

and mild AD.[58] One trial has been completed using tDCS for neuropsychiatric symptoms of dementia, although the results are currently unavailable.[59]

- Also in the recruitment phase, another team in Ontario is investigating the role of rTMS for comorbid depression and cognitive impairment in older adults.[60] A team in Manitoba is investigating rTMS as a treatment for AD and are also still in the recruitment phase.[61] There are 2 clinical trials that have been completed investigating rTMS — 1 in Ontario for participants with early AD[62] and 1 in Manitoba investigating the impact on AD and sleep quality,[63] although the results are not yet available. A trial completed in 2018 in Ontario investigated the impact of paired associative stimulation, both electrical stimulation and TMS, in patients with mild AD, although the results are also unavailable.[64]

Internationally, the approval landscape is similar to that in Canada. Many of the techniques have been approved for other conditions but not for AD. In the US, for example, the FDA has approved the use of TMS technology for the treatment of migraine and VNS for the treatment of depression and epilepsy but not for AD;[25] although, as discussed previously, many devices have received Breakthrough Device designation and/or are in the process of completing clinical trials before seeking FDA approval.[20,47,48,54] Additionally, as of April 1, 2021 the NHS recommends the use of transcranial magnetic resonance–guided focused ultrasound technology for the treatment of medication-refractory essential tremor, but the same cannot be said for AD.[65]

Cost and Administration

Given the variability in application methods for the different neuromodulation techniques, costs vary. For example, tDCS technology has been noted as being cheaper than rTMS technology.[27] Furthermore, the invasive techniques might be more expensive than external devices due to the necessary surgery involved in the techniques. For VNS, while approved in the US for other conditions, its implementation has been limited both because of the cost and the invasive nature of the technology.[25] Furthermore, likely since the devices are still under investigation for AD, insurance policies have yet to deem technologies medically necessary for AD, despite their recognition of their use for other conditions, such as DBS for Parkinson disease or TMS for major depressive disorder.[66,67] Without coverage, if patients were to use the device for AD, it would be paid for out of pocket.

If found to be effective for AD, the in-home applicability of some of the devices is also attractive from a societal cost perspective. Compared to invasive techniques, noninvasive neuromodulation technologies have the benefit of potentially being able to be delivered completely at home. As with any surgical intervention, DBS and VNS expose patients to potential surgical complications and, although the surgeries are minimally invasive, patients and caregivers must travel to the hospital (potentially in a different community or city) to receive the interventions and likely for follow-up visits. Both tACS and tDCS devices have been reported as feasible to use in the home setting, reducing costs related to travel to health care centres and hospital stays, and users can use the devices at their convenience — ideally minimally impacting regular routines.[27,39] Although this would require training for the caregivers, it has been reported that the training is not difficult and virtual support is available to help with the training process.[39]

Operational Considerations

Uptake

Ethical Considerations

Given the cognitive ability of patients who live with AD, ethical considerations regarding a person's ability to provide informed consent has raised some concerns for the more invasive techniques, notably DBS.[9,68] Ethicists are specifically concerned regarding the ability of patients with severe AD to provide consent. Merlin Bittlinger, a research fellow and ethicist at the Berlin Institute of Health, has stated that older adults with severe AD should not be allowed to undergo DBS, as the level of dementia in these patients hinders autonomous-informed consent.[68] Additionally, reports of some patients experiencing self-estrangement, psychological or psychiatric effects, and altered social relations after DBS have raised ethical concerns for the potential harms of the procedure.[9]

Safety

People with AD and their families may also be more likely to want to use noninvasive techniques over the invasive techniques. Although preliminary results suggest that all the 10 neuromodulation techniques discussed in this report are safe, whether or not to expose an older individual to a surgical procedure is a common conundrum. Two non-randomized studies including elderly patients with dementia undergoing major surgery reported higher risks of mortality, non-home discharge, complications, and prolonged hospitalization compared to patients without dementia.[69,70] Notably, postoperative delirium was highlighted as a postoperative concern after any procedure, with the occurrence higher among patients with pre-existing dementia and which was found to be strongly associated with longer hospital stays and urgent operations.[65] Some studies have also reported an increased risk of dementia or mild cognitive impairment following surgery in healthy older patients, although the research is inconclusive.[71] The uncertainty of potential side effects of any surgery among individuals who are potentially frail may have an impact on the uptake of the more invasive techniques.

Lack of Effective Treatments

Although some pharmaceuticals are being approved through accelerated application processes to increase treatment options available, the evidence on their effectiveness is still unclear and pharmaceuticals tend to be costly for the consumer.[72] Given the lack of effective treatments for AD, people with AD and their families are likely motivated to find treatments that work, particularly considering that the condition affects a person's ability to independently complete daily activities.[11] The burden placed on family members while also dealing with the pain of watching a loved one struggle makes finding more effective treatments for the disease important. Most of the technologies reviewed in this report can be used on their own, potentially offering alternatives to the available pharmaceutical treatments that are costly and currently have unclear effectiveness. Additionally, evidence suggests that although adding neuromodulation techniques to cognitive treatment is safe, the cognitive training does not provide any additional effect, suggesting that neuromodulation may be used on its own.[27]

Perspectives to Consider

Due to the nature of AD and the reliance of many on unpaid caregivers, family members or friends, and paid caregivers, it is important to consider the perspectives of all those involved in the care of AD patients for the potential uptake of these technologies. For studies that

evaluated the potential of devices to be delivered at home, the patient or caregiver received training on the use of the device, which would take time and could place a burden on the caregiver to ensure the device is used correctly.[27,39] Important considerations that were not highlighted in the literature was whether supervision is required when using the devices at home or whether there is a recovery period after invasive techniques that requires more attention from the caregiver. Caring for loved ones living with AD can be a burdensome task[11] and the impact of these technologies on the caregiver are important considerations.

Final Remarks

Ten different neuromodulation techniques were described in this report — 2 invasive and 8 noninvasive stimulation techniques — and only a few with direct evidence for the treatment of any stage of AD. Overall, the majority of published studies for all included neuromodulation techniques were completed with small sample sizes.[6,16,33] Furthermore, most of the techniques described in this report are new approaches in the treatment of AD, limiting the quantity of evidence available. Most of the conclusions are supported by promising preliminary results among patients with AD and demonstrated success of the neuromodulation techniques in similar disorders, but studies with adequate sample size that can determine the effectiveness of the interventions for AD need to be completed to understand the potential roles of the various neuromodulation interventions for people with AD.

The heterogeneity of the pathogenesis and symptoms of AD suggest the need for a wide variety of potential treatments. The 10 identified neuromodulation techniques described in this report all provide promising preliminary results and, if found to be effective, may offer people with AD a choice of treatment that suits their needs. Given the increasing impact of AD on people living in Canada, the pursuit of more effective treatments is critical.

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