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Better language through chemistry: Augmenting speech-language therapy with pharmacotherapy in the treatment of aphasia

Melissa D. Stockbridge

Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21287

Abstract

Speech and language therapy is the standard treatment of aphasia. However, many individuals have barriers to seeking this measure of extensive rehabilitation treatment. Investigating ways to augment therapy is key to improving post-stroke language outcomes for all patients with aphasia, and pharmacotherapies provide one such potential solution. Although no medications are currently approved for the treatment of aphasia by the United States Food and Drug Administration, numerous candidate mechanisms for pharmaceutical manipulation continue to be identified based on our evolving understanding of the neurometabolic experience of stroke recovery across molecular, cellular, and functional levels of inquiry. This chapter will review evidence for catecholaminergic, glutamatergic, cholinergic, and serotonergic drug therapies and discuss future directions for both candidate drug selection and pharmacotherapy practice in people with aphasia.

Keywords

pharmacotherapy; adjunctive therapy; neural plasticity; memantine; SSRI; levodopa; donepezil; amantadine

Introduction

Speech and language therapy (SLT) is the standard treatment of aphasia (Kurland et al., 2012), and prior work suggests that about 100 hours of SLT are needed to significantly improve functional communication (Bhogal et al., 2003). However, many individuals have barriers to seeking this measure of extensive rehabilitation treatment. For example, they may no longer be able to drive and have difficulty coordinating the logistics of frequently visiting a doctor's office, or they may have financial constraints to ongoing therapy. Thus, identifying ways to provide the most effective and efficient SLT and investigating ways to augment SLT through other means are key to improving post-stroke language outcomes for all patients with aphasia. Many authors have highlighted the value of synergistic approaches to post-stroke recovery that augment behavioral SLT, using behavioral therapies and other noninvasive ways of stimulating activity in brain areas of the task-specific network

Address Manuscript Correspondence to: Melissa D. Stockbridge (md.stockbridge@jhmi.edu), Department of Neurology, 600 North Wolfe Street, Phipps 4, Suite 446, Baltimore, MD 21287.

(e.g., repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tCDS)) with pharmacologic interventions (Llano and Small, 2016; Bao et al., 2001; Korchounov and Ziemann, 2011). However, while noninvasive brain stimulation has provided a rich and clear path of clinical inquiry (Saxena and Hillis, 2017), identifying which drugs to utilize for cognitive-linguistic augmentation in this population is far less clear.

No medications are currently approved by the United States Food and Drug Administration (FDA) for the treatment of aphasia, and there are relatively few studies of drug therapy. Candidates for pharmaceutical intervention to restore function are based on our limited, yet evolving, understanding of the neurometabolic mechanisms of stroke recovery across molecular, cellular, and functional levels. While some regeneration does occur, synaptic plasticity is believed to be the dominant mechanism for recovery. This provides many targets for pharmaceutical intervention to improve outcomes. Treatment for aphasia has focused on modifying strength and excitability of existing synaptic pathways between the forebrain and areas necessary for language in the cerebral cortex. Existing synaptic connections can be modulated by long-term potentiation (LTP), long-term depression (LTD), and spike timing-dependent plasticity (STDP) via noradrenergic, cholinergic, dopaminergic, and serotonergic pathways. Glutamate (Malykh and Sadaie, 2010) and γ-aminobutyric acid (GABA) have been implicated in language processing as well (Berthier et al., 2011a). Activity-dependent mechanisms also include axonal sprouting (Dancause et al., 2005; Overman et al., 2012; Carmichael et al., 2017) and dendritic spine elaboration (Brown and Murphy, 2008; Ueno et al., 2012), and migration of subventricular stem cells to peri-infarct regions (Danilov et al., 2012; Wang, 2014; Merson and Bourne, 2014).

Perhaps it is because of our dynamic understanding of stroke and recovery that it is noteworthy to list pharmacotherapies that have been shown to be harmful to post-stroke cognition and language. Barbiturates (Linn and Stein, 1946; Linn, 1947; Bergman and Green, 1951; D'Asaro, 1955), carbamates (West and Stockel, 1965), dopamine antagonists (Feeney et al., 1982; Feeney and Hovda, 1983; Porch et al., 1985), norepinephrine-dopamine reuptake inhibitors (Darley et al., 1977), benzodiazepines (Darley et al., 1977), and alpha blockers (Llano and Small, 2015) all have demonstrated deleterious effects on post-stroke recovery.

Many pharmaceutical candidates for language augmentation after stroke have been vetted in animal models using motor recovery as the primary outcome variable (Llano and Small, 2016). The reliance on animal models results in limited generalizability with regard to aphasia (Hauser et al., 2002); no known intervention results in a mouse that can score within the healthy range on any common assessment of language. An encompassing view of cognitive and linguistic improvement necessitates the more lengthy, complex, messy, and expensive involvement of human subjects.

While early work focused on catecholamines (epinephrine, norepinephrine, dopamine) underlying synaptic plasticity, more recent advances have centered on therapies that target other neurotransmitters and modulators (glutamate, acetylcholine, serotonin) as promising candidates. That said, the leading edge of the broader landscape of post-stroke drug

therapies encompasses a staggering array of investigative directions, including growth factors (Lee et al., 2005; Zhao et al., 2007) and C-C chemokine receptor 5 inhibitors (Joy et al., 2019). Unfortunately, the vetting of these therapies in humans is, at best, ongoing (Kumar and Kitago, 2019), and it is likely to be some years before they can be considered when addressing the relatively narrow problem of post-stroke language deficits. Comprehensive surveys of the landscape of drug trial histories in cognitive and linguistic recovery from stroke are far more abundant and contemporary than clinical trials (Saxena and Hillis, 2017; Small, 1994; Llano and Small, 2015; Llano and Small, 2016; Keser and Francisco, 2015; Engelter, 2013; Shisler et al., 2000; Small, 2004; Berthier, 2005; de Boissezon et al., 2007; Lee and Hillis-Trupe, 2008; Floel and Cohen, 2010; Berthier et al., 2011b; Cahana-Amitay et al., 2014; Ramezani et al., 2015; Liepert, 2016; Walker-Batson et al., 2016; Kumar and Kitago, 2019), recently emerging at the rate of about one per year. As such, this chapter will attempt to build upon this comprehensive discussion by providing a more speculative discussion of future directions for candidate drug selection, as well as a broader discussion of pharmacotherapy practice in people with aphasia.

Catecholamines

When considering catecholamines in the treatment of aphasia, it is important to stress that norepinephrine and dopamine have been shown to modulate the fundamental mechanisms of learning and memory (Asanuma and Pavlides, 1997; Korchounov and Ziemann, 2011; Ripollés et al., 2018): LTP (Dommett et al., 2008; Gu, 2002; Otani et al., 2003; Calabresi et al., 2007; Calabresi et al., 2006), LTD (Clem and Huganir, 2013; Cahill and Milton, 2019), and STDP (Edelmann and Lessmann, 2013; Sjostrom et al., 2008; Froemke et al., 2005). Catecholamine concentration decreases in the brainstem, subcortex, and cortex following ischemia (Brown et al., 1974; Cohen et al., 1975; Robinson et al., 1980). Dopamine appears to play a critical role in facilitating functional compensation by the non-infarcted hemisphere (Obi et al., 2018). Remedying this deficit to better support stroke recovery (Feeney and Westerberg, 1990) has been a vigorous investigative direction resulting in mixed and modest evidence of improvement in aphasia.

Stimulants, such as dextroamphetamine, cause the release of the presynaptic catecholamines, norepinephrine and dopamine (Feeney et al., 1982), as well as serotonin. However, their use for cognitive enhancement well predates this understanding. Amphetamine salts were used clinically since the 1920s and, in the 1940s, they became the first drugs approved for the treatment of mild depression (Rasmussen, 2006). While structurally similar to amphetamine, methylphenidate blocks reuptake of norepinephrine and dopamine in presynaptic neurons, resulting in milder stimulant effects (Rowe and Kurczewski, 2018). In healthy adults, prior studies have shown improved word learning with dexamphetamine (Whiting et al., 2007; Whiting et al., 2008; Breitenstein et al., 2006), as well as the potential for broader cognitive enhancement (Ilieva et al., 2015; Smith and Farah, 2011). Evidence of post-stroke motor recovery is mixed (Feeney et al., 1982; Keser and Francisco, 2015; Feeney and Hovda, 1983; Hovda and Fenney, 1984). There are small but significant effects of dextroamphetamine-assisted SLT on language performance on the Porch Index of Communicative Ability (PICA) (Walker-Batson et al., 2001) and confrontation naming (Whiting et al., 2007). Methylphenidate yielded no improvement on the PICA (Darley et al.,

1977). Patients who received 10 mg dextroamphetamine for one week in conjunction with tDCS and speech therapy saw a benefit of stimulant over placebo on the bedside Western Aphasia Battery (WAB) (Shewan and Kertesz, 1980; Keser et al., 2017). Case studies have contributed to the body of evidence that stimulants may improve overall language performance (Walker-Baston et al., 1991; Spiegel and Alexander, 2011); however, modest results, lack of replication of positive results, and the need to mitigate hypertension in the post-stroke population have led to recommendations against this intervention (Martinsson et al., 2007).

Levodopa (an aromatic amino acid) is the metabolic precursor to dopamine, norepinephrine, and epinephrine. It is supplied in combination with carbidopa, an aromatic amino acid decarboxylation inhibitor, and it is approved for use in the treatment of Parkinson's disease and syndrome. Recent studies using levodopa in conjunction with SLT have demonstrated that it facilitates word learning in healthy individuals (Knecht et al., 2004; Breitenstein et al., 2006; Shellshear et al., 2015). Levodopa combined with SLT, five days a week for three weeks, resulted in no significant improvements on the Boston Diagnostic Aphasia Examination (Seniów et al., 2009), but trended toward significance in those with frontal lesions. Unfortunately, randomized-double-blind controlled crossover studies, in both acute aphasia (Leemann et al., 2011) and chronic aphasia (Breitenstein et al., 2015), have not yielded evidence of any benefit over placebo.

Dopamine agonists (e.g., apomorphine, bromocriptine) also have been investigated in conjunction with SLT. Bromocriptine functions on mesocortical dopaminergic neurons projecting to the basal ganglia, supplementary motor area, and anterior cingulum (Ramezani et al., 2015), and it has an approved indication for use as an adjunctive treatment to levodopa in individuals with late stage Parkinson's disease. Although studied in post-stroke aphasia, there is minimal evidence that bromocriptine paired with SLT is associated with language improvements (Gill and Leff, 2014), perhaps due to the fact that lesions associated with aphasia do not typically involve these regions. Studies vary widely in their recruitment and methodologies. In the acute phase, there is no evidence that people with non-fluent aphasia improve more with bromocriptine than placebo (Ashtary et al., 2006), particularly if their deficits are moderate to severe. In the chronic phase, a number anecdotal studies seem to show increased word finding, verbal fluency (Sabe et al., 1992; Gold et al., 2000), reading comprehension, and repetition (Bragoni et al., 2000), while randomized, double-blind, placebo-controlled crossover studies observed no such effects, with (Sabe et al., 1995) or without (Gupta et al., 1995) SLT.

Amantadine, a dopamine agonist indicated to treat parkinsonism and Influenza A, also has attracted interest. It is associated with improved verbal fluency in a patient with post-hypoxic encephalopathy and transcortical sensory aphasia (Arciniegas et al., 2004). Four other patients with transcortical motor aphasia showed improvements with amantadine (Barrett and Eslinger, 2007). However, amantadine has not been the subject of further study, possibly because of its numerous central nervous system side effects, drug interactions, low acute lethal dose, and dosage and administration concerns for patients with renal impairment, liver disease, congestive heart failure, and other conditions more frequently found in geriatric patients.

Null findings in catecholamine studies may be due to ceiling effects associated with sufficiently intensive SLT co-occurring with drug treatment, which suggests further large-scale clinical trials are needed to examine the interaction of catecholamines and SLT dosage on language improvements (Saxena and Hillis, 2017). However, overall enthusiasm for treatment of aphasia via this pathway is tempered by the combination of mechanistic evidence against the likelihood of efficacy for aphasia and frequent null-results in the relatively limited randomized double-blind controlled trials. Enthusiasm also is limited by dose-limiting adverse reactions, including frequent nausea, dystonic movement, and lack of energy (Sabe et al., 1995; Bragoni et al., 2000), which have resulted in discontinuation of therapy. From a practical standpoint, the benefit versus risk often is not favorable to the patient.

Glutamate and GABA

Glutamate and its derivative, GABA, have a tightly regulated homeostasis in the brain, with excitatory glutamate and inhibitory GABA receptor pathways. Regulation of the ionotropic glutamate receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA), play a role in learning and memory. For example, spike-timing dependent plasticity involves changes in synaptic activity at glutamate receptors (Foncelle et al., 2018; Sjostrom et al., 2008; Feldman, 2012). Following stroke, the peri-infarct region experiences increased extracellular GABA, resulting in hypoexcitability (Brickley and Mody, 2012). Thus, another pharmacologic strategy for aphasia therapy would be to block GABA or to increase glutamatergic signaling.

Piracetam, a GABA derivative thought to modulate AMPA and NMDA receptors, has been a subject of investigation in aphasia along with other racetams (Malykh and Sadaie, 2010). In the largest multicenter, randomized, double-blind study on piracetam in stroke to date (Piracetam in Acute Stroke Study; PASS), 927 patients were treated with 12 g of intravenous piracetam over 20 minutes or placebo within the first 12 hours after stroke followed by 12 g daily for 4 weeks then 4.8 g daily for 8 weeks. Results on the Orgogozo scale, a measure of function (Orgogozo et al., 1983), at four weeks did not differ between groups (De Deyn et al., 1997). However, within a small subgroup of patients who received piracetam within seven hours following moderate or severe stroke (n = 360), piracetam administration did result in significant benefit. Of note, while the Orgogozo scale captures verbal communication among an array of other activities, rating from 0 for “impossible” to 10 for “normal,” the authors did not parse the overall scale scores by activity. When patients from the PASS who had aphasia (n=373) were examined after the fact, 10% more of those who received piracetam had “recovered” from aphasia by 12 weeks versus placebo. Among those who received the dose within the first 7 hours, there was a 16% difference between groups (Orgogozo, 1999).

A contemporary meta-analysis found no statistically significant effect of piracetam on aphasia impairment (Zhang et al., 2016), echoing numerous findings of null effects (Huber et al., 1997; Güngör et al., 2011). It is possible that differences in outcome measures and duration of subscription could account for findings in favor of piracetam use in aphasia (Tanaka et al., 2001; Huber, 1999; Enderby et al., 1994), particularly when combined with

intensive SLT (Huber et al., 1982) to facilitate changes in perfusion (Kessler et al., 2000). Racetam studies in aphasia are ongoing (e.g., NCT00227461).

Brain-derived neurotrophic factor (BDNF) increases NMDA receptor activity, playing a major role in regulating synaptic transmission and plasticity in adults (Gottmann et al., 2009; Bramham and Messaoudi, 2005; Foncelle et al., 2018; Edelmann et al., 2014; Park and Poo, 2013). Memantine is a non-competitive NMDA receptor antagonist that increases the production of BDNF (Sonkusare et al., 2005), thus improving glutamatergic transmission, which is thought to make remaining neural networks more efficient in moderate-to-severe Alzheimer's dementia (Parsons et al., 2007). In patients with chronic post-stroke aphasia, 16 weeks of memantine (20 mg/day) without SLT improved WAB performance. When patients received an additional two weeks of constraint-induced aphasia therapy, improvements over placebo were even greater. Even after memantine was discontinued, patients who had received memantine retained a significant improvement in WAB scores over the placebo group, although the difference in scores had diminished, suggesting that gains were not stable long term (Berthier et al., 2009). While actual differences in scores were small, adding to the enthusiasm surrounding memantine is its profile of relative safety and tolerability, even when combined with other medications (Berthier and Pulvermüller, 2011).

Acetylcholine

Acetylcholine promotes neural plasticity (Foncelle et al., 2018) through the induction of LTP and LTD (Sarter and Parikh, 2005), which has led to its focus as a mechanism for post-stroke recovery in the last 20 years. It also appears to have particular implications for language. Cholinergic activity is greater in the left brain than right brain (Amaducci et al., 1981; Glick et al., 1982), and there is a relatively high density of acetylcholinesterase-containing axons within primary auditory regions and posterior cortical regions associated with language (Hutsler and Gazzaniga, 1996). It is not surprising then that scopolamine, a commonly used perioperative *anti*cholinergic therapy, impairs non-word reading, word and non-word spelling, and verbal fluency in healthy adults (Aarsland et al., 1994), deficits not related to arousal.

Development of cholinergic pharmaceuticals has centered on their use in Alzheimer's dementia, a neurodegenerative disease with cognitive impairment that is associated with a loss of cholinergic neurons (Whitehouse et al., 1981). Reversible cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine), which block the breakdown of acetylcholine by cholinesterase enzymes, were the first (Plaitakis and Duvoisin, 1983; Heinrich and Teoh, 2004), and now the most common, means of enhancing synaptic acetylcholine to improve memory (Birks and Harvey, 2018). As with post-stroke aphasia, there are currently no drugs approved by the FDA for primary-progressive aphasia, the syndrome of progressive neurodegenerative impairment with central language features. Primary-progressive aphasia has been a proposed target for cholinergic therapies due to its relationship with Alzheimer's disease (Schaeverbeke et al., 2017; Ferris and Farlow, 2013), but findings so far do not support their use. An open-label randomized, placebo-controlled study saw a trend toward stabilization of WAB aphasia quotient (WAB-AQ) in patients with primary-progressive aphasia (N=20) who received galantamine for 26 weeks (Kertesz et al., 2008); however

cholinesterase inhibitors most often have been associated with worsening of symptoms (Mendez et al., 2007) and more frequent cognitive adverse reactions (Boxer et al., 2013).

Cholinergic pharmacotherapies for post-stroke aphasia therapy have shown positive results, with improvements noted in overall language production, repetition, naming, and auditory comprehension (Zhang et al., 2018). However, to our knowledge, no papers have contextualized results with clinical significance, nor have improvements consistently been greater than expected variability among administrations of a utilized testing instrument (i.e., test-retest reliability). Much of what is known about cholinergic potentiation in aphasia is to the credit of a single dedicated group investigating donepezil, Marcelo Berthier and colleagues who have been supported by Pfizer Spain and Eisai (makers of Aricept) in their work for over a decade. In their double-blind randomized, placebo-controlled study of 26 patients with chronic post-stroke aphasia, taking 10 mg/day of donepezil for 16 weeks with SLT, there was significant improvement in WAB-AQ, picture naming, and spousal ratings of communication activities of daily living (Berthier et al., 2006), confirming findings from an earlier sampling of 11 patients who participated in a 20-week open-label study (Berthier et al., 2003). It was noted that improvements were no longer present when reassessed at 20 weeks.

Other groups have reported similar findings when patients were treated with donepezil over a 12-week span. Small but significant improvements on the WAB-AQ were seen in patients with acute aphasia (Ying et al., 2010)† and in a mixed sample (Haixia and Shilin, 2014)†, for whom improvements endured beyond the discontinuation of the drug. Small but significant improvement on the WAB-AQ also was noted among those with chronic post-stroke aphasia receiving galantamine (Hong et al., 2012). The authors identified subcortical dominant lesion pattern, cognitive performance at baseline, and higher levels of education as significant determinants of good responsiveness to galantamine (defined as a WAB-AQ increase of 20 points or more).

The following open-label studies and case reports also have contributed to our current knowledge base for cholinergic therapy in post-stroke aphasia, particularly when addressing aphasia subtypes and atypical etiologies:

- Two patients with sub-acute Wernicke’s aphasia, receiving bifemelane (300 mg/day) with SLT, showed significant increases in category fluency and picture naming, language scores that correlated significantly with acetylcholinesterase measured in cerebrospinal fluid (Tanaka and Miyazaki, 1997). Bifemelane is a monoamine oxidase inhibitor (MAOI) that increases cortical and hippocampal acetylcholine (Saito et al., 1985).
- A patient with severe chronic post-stroke Wernicke’s aphasia improved in both WAB-AQ and general cognition 3 months after a 6-week course of donepezil (Yoon et al., 2015).

†Full-text versions of these articles were not available in English as of May 2020. Descriptions of these findings are based on English-language abstracts available via aggregated databases. Although findings are included where relevant, methodologies and results could not be critically reviewed.

- Three patients with chronic post-stroke conduction aphasia, receiving donepezil (5 mg/day for 4 weeks then 10 mg/day for 12 weeks) combined with SLT (massed sentence repetition therapy), showed improved language production on the WAB-AQ over SLT alone (Berthier et al., 2014).
- A patient with severe Broca's aphasia and moderately severe apraxia 18 months post-stroke, receiving donepezil (5 mg/day for 6 weeks), improved slightly in word repetition, attention, and motor speech directly following treatment and at 25.5 months post-stroke (Pashek and Bachman, 2003).
- Four post-stroke patients with apraxia, receiving donepezil (5 mg/day) with 10 mg dextroamphetamine administered 30 minutes prior to each 1.5 hour SLT session (36 hours/week for 6 weeks), had improved scores on the PICA. Due to the open label, pilot study design, differentiating the effects of SLT, either drug therapy, or the combination was not possible; however, the authors noted that gains were maintained after the treatment period (Walker-Batson et al., 2016).
- Following a right striatal-capsular hemorrhage, a patient with noted atypical brain-language organization, who experienced chronic language deficits and post-stroke depression that was treated escitalopram (a selective serotonin reuptake inhibitor, SSRI), first received donepezil then donepezil combined with SLT (Berthier et al., 2017). The patient's other ongoing pharmacological treatments, including baclofen and levetiracetam, were kept unchanged during the trial. When receiving donepezil without SLT (5 mg/day for 4 weeks, then 10 mg/day for 12 weeks), the patient improved significantly over baseline on WAB-AQ, connected speech, and word repetition. Although performance slightly improved when SLT was included, the differences in these measures between the donepezil trial and the combined donepezil and SLT trials were not significant.
- One prior study also examined the combination of donepezil with an SSRI (fluoxetine) in 48 patients with aphasia receiving SLT, finding that the combined treatment improved WAB-AQ over donepezil alone (Dong et al., 2016)[†].

These findings highlight the need for large-scale randomized controlled clinical studies, such as the upcoming investigation of donepezil combined with transcranial direct current stimulation (NCT04134416), meta-analyses, and comprehensive analyses of clinically meaningful differences. Multiple studies also failed to differentiate between a potential direct benefit from cholinergic stimulation on cognition and language and the secondary benefits associated with ameliorating post-stroke depression. Dampening enthusiasm with this pharmacotherapy is evidence that increasing synaptic acetylcholine may negatively impact language. In one recent double-blind placebo-controlled cross-over study, donepezil was associated with a harm to speech comprehension among patients with chronic post-stroke Wernicke's aphasia (Woodhead et al., 2017). Moreover, nearly all reported studies suffered considerable attrition due to poor drug tolerance, echoing the observation that cholinesterase inhibitors frequently cause nausea, vomiting, anorexia, diarrhea, and dizziness as a result of cholinergic overstimulation (Ali et al., 2015).

Serotonin

Serotonin also has been shown to play a role in enhancement of synaptic plasticity, neurogenesis, synaptogenesis, and dendritic remodeling (Kuo et al., 2016; Sodhi and Sanders-Bush, 2004; Jitsuki et al., 2011; Vetencourt et al., 2011; Brezun and Daszuta, 2000; Santarelli et al., 2003; Karpova et al., 2011; Wang et al., 2008). BDNF promotes the development and function of serotonergic neurons, and selective serotonin uptake inhibitors (SSRIs) increase BDNF gene expression (Martinowich and Lu, 2008). While amphetamines and other non-selective serotonin agonists activate receptors directly, SSRIs and MAOIs increase extracellular serotonin indirectly. Numerous SSRIs (e.g., fluoxetine, escitalopram, fluvoxamine) and MAOIs (e.g., isocarboxazid, selegiline, tranylcypromine) have been FDA-approved for use in treating major depression disorder and other related affective and mood disorders and are generally preferred to catecholaminergic therapies. Studies have shown a positive effect of SSRIs on post-stroke motor recovery when administered acutely (in the FLAME study, a large double-blind, placebo-controlled phase II trial, Chollet et al., 2011; Pariente et al., 2001; Marquez-Romero et al., 2020; Asadollahi et al., 2018) and in the chronic phase (Zittel et al., 2008). There also is evidence of improvement in cognitive recovery (Jorge et al., 2010), but not in coarse measures of overall disability (Dennis et al., 2019) or functional recovery (Kraglund et al., 2018). A recent Cochrane review found statistically significant benefits of SSRI in reducing dependency at the end of treatment, improving neurologic deficits and affect, but not overall measures of cognition (Mead et al., 2012). An updated meta-analysis of 1549 patients found that SSRI use was associated with better overall recovery and functional independence (Gu and Wang, 2018).

The effects of SSRIs on post-stroke aphasia recovery are promising. In a double-blind, randomized crossover trial, 10 patients with fluent post-stroke aphasia, receiving fluvoxamine for 4 weeks, improved in picture naming on the BNT and had reduced perseverations (Tanaka et al., 2004); but, no changes were observed on the WAB or a number of other language measures. In a cross-sectional study of 45 patients with left hemisphere ischemic stroke, when matched for similar age, time post-onset, and education, patients who were given antidepressants from onset of stroke through recovery had significantly higher repetition scores than those who had not, even though they had larger infarcts on average (Hillis and Tippett, 2014). Groups did not differ in total WAB score. WAB Quartile in the chronic phase was predictable by a model that included education, volume of infarct, antidepressant use, and age, all of which were significant predictors. A second multicenter cross-sectional study of chronic aphasia found that individuals who continuously used SSRIs for the first three months following stroke had greater frequency of improved picture naming and inclusion of more elaborate content when describing a picture than those with similar initial aphasia severity, similar levels of depressive symptoms, and similar lesion volume and percentage of damage to important regions for language function (Hillis et al., 2018).

In contrast, a randomized, double-blind, placebo-controlled trial, administration of an MAOI (moclobemide), beginning around 18 days post-stroke and continuing for 6 months (without SLT), did not improve performance on the Amsterdam Nijmegen Everyday Language Test of verbal communication or Reinvang's *Grunntest for Afasi* (a test similar to the WAB) over

placebo (Laska et al., 2005). This null result may be due to the absence of controlled or high-intensity SLT during the drug trial period, as recent reviews have suggested the effects of SSRIs on post-stroke plasticity are experience-dependent (Schneider et al., 2019).

While their benefits to cognitive recovery appear to be independent of SSRIs' mitigation of post-stroke depression (Jorge et al., 2010), this finding does not downplay the deleterious effect of depression itself on the post-stroke experience. One in five patients with stroke will develop depression (Barker-Collo, 2007), which can directly impact cognitive-linguistic performance (Narushima et al., 2003; Okon-Singer et al., 2017; Smirnova et al., 2018; Rude et al., 2004; Kimura et al., 2000) and engagement with SLT (Skidmore et al., 2010). It is possible that SSRIs could benefit patients' overall communication and social participation directly and indirectly through changes to language, cognition, and mood. Multiple studies of SSRIs on stroke outcomes are ongoing (NCT02737930, NCT04221256, NCT02767999, Graham et al., 2017), and trials specifically targeting SSRI use in aphasia therapy are planned (NCT03843463).

Final Thoughts

Over the last 70 years and beyond, our ability to treat aphasia has improved through our evolving understanding of healthy neurophysiology and the metabolic experience of stroke. While undeniable progress has been made in the behavioral treatment of aphasia through SLT, clinical trials have been slow to provide evidence of safe and effective gains in cognition and language through drug treatment that would support clear recommendations for people with post-stroke aphasia. Despite the limited evidence to date, there are emerging candidates for adjunctive pharmacotherapy that provide exciting prospects for further large-scale, double-blind trials and may be appropriate for clinicians to consider in the interim practice of medicine. For example:

- In chronic post-stroke aphasia, memantine combined with SLT over time appear to improve language recovery. Memantine is relatively safe and well-tolerated, even when combined with other medications.
- Early evidence suggests SSRIs appear to have variable but broad benefits to linguistic, cognitive, and functional recovery in the acute and chronic phase following stroke, in addition to their effect on mood. Clinical trials, currently in recruitment, will further our understanding of this generally well-tolerated drug class beyond treatment of post-stroke depression.
- Levodopa and donepezil should be the subjects of further, more rigorous study. While the majority of dopamine agonists have not proven themselves in the existing trials, limited data on amantadine has shown promise and should be investigated further.

These selections highlight another changing aspect of pharmacotherapy in stroke rehabilitation. Early clinical trials primarily focused on brief, finite subscription windows (Shewan and Kertesz, 1980; Orgogozo, 1999). However, increasingly, studies have included longer windows of subscription (Seniów et al., 2009; Huber et al., 1997), approaching maintenance terms (Güngör et al., 2011; Berthier et al., 2009; Hong et al., 2012; Hillis et al.,

2018; Kertesz et al., 2008). Longer treatments are rational, as numerous neurodegenerative and chronic conditions are generally treated in this therapeutic model. The decline in stroke mortality (Lackland et al., 2014) has increasingly demanded that stroke be conceptualized as a chronic and progressive disabling disease (Carmichael, 2016), treated primarily through maintenance medication (Gallacher et al., 2014). Some authors have minimized pharmacotherapies that nominally confer benefits that fail to endure after therapy is discontinued and eliminated (Llano and Small, 2016; Small and Llano, 2009). While this is a noble ideal, if we change our model, and thus our definition of success, from endurance of functional language improvements gained during adjunctive pharmacologic therapy during SLT to *maintenance* of SLT-driven cognitive-linguistic gains through the ongoing use of pharmacology, previously dismissed therapies gain a new potential for improving the lives of people with aphasia.

These conditions further require practitioners to critically consider the issue of appropriate polypharmacy in the aging population. While recent work has considered the synergistic use of multiple drugs in post-stroke recovery (Walker-Batson et al., 2016; Dong et al., 2016), polypharmacy contributes to an increased risk of medication error and poor compliance (Stawicki and Gerlach, 2009), and it should be avoided where unnecessary (Llano and Small, 2015). Artfully combined use of pharmacotherapy, SLT, and stimulation as a means to shift synaptic thresholds (i.e., rTMS, tDCS) likely will shape the future of cognitive-linguistic rehabilitation.

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