CHOLINESTERASE INHIBITORS: A LITERATURE REVIEW OF MEDICATION EFFICACY AND SAFETY FOR ALZHEIMER'S DISEASE

Ashley Wicklund, PA-S2, B.A.(Hons)

7614995
umkrychu@myumanitoba.ca

Supervisors: Dr. Vishal Raj Kaushik, BSc (Pharm), MD, FRCPC and Melanie Richard, CCPA, MPAS, MSc, BSc

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Abstract

Background: With a steady increase of seniors in Canada's overall population, geriatric-associated illnesses such as Alzheimer's disease (AD) will continue to rise. AD is a progressive neurodegenerative disorder that causes plaque build-up in the brain and subsequent cerebral atrophy. Currently, there are no treatments marketed to cure the disease, but rather to provide symptomatic relief. Cholinesterase inhibitors have been approved by the US FDA for mild, moderate, and severe AD. Previous studies have investigated the efficacy and safety profile of these medications.

Methods: This literature review assessed existing meta-analyses using the PubMed database from 2015-2020 using search terms 'cholinesterase inhibitors effectiveness' and 'Alzheimer's'. Outcomes included adverse events associated and change in cognitive function.

Results: Five articles met the criteria for the study. All studies concluded there was at least mild or slight improvement on cognitive function with the use of the cholinesterase inhibitors and risks of adverse events were somewhat increased with their use but were likely mild.

Conclusion: Given the mild improvement in cognitive functioning coupled with an overall increase in adverse events when compared to placebo, this risk-benefit relationship demonstrates mild evidence in their utility in Alzheimer's Disease. However, due to the heterogenicity of the available literature, further high quality studies would be ideal to further explore their efficacy in Major Neurocognitive Disorder (NCD) due to Alzheimer's Disease.

Introduction

According to Statistics Canada, the proportion of seniors (65 years and older) within our national population has been steadily increasing since 1960 from 8% of the total population to 17.5% as of July 2020[1]. This proportion is projected to continue to rise, and seniors are expected to comprise ~25% of the population by 2036. With this steady increase in our population, we anticipate to see an increase in chronic and geriatric-based illnesses, which render them as important topics to further study and to understand in order to help with management.

According to the Alzheimer Society of Canada, in 2016 there were an estimated 564,000 Canadians living with dementia (Major Neurocognitive Disorder) and it is expected that by 2031, an increase of 66% to 937,000 Canadians will be seen[2]. Furthermore, the estimated combined cost of dementia (both for the healthcare system and out-of-pocket costs) was estimated to be $10.4 billion in 2016 and is expected to rise upwards towards $16.6 billion by 2031[3]**.** Remarkably, the national Omnibus

survey report for the Alzheimer Society of Canada from 2018 reported that over half of Manitobans are impacted by dementia because they have a family member or close personal friend with the disease[4]**.** This provides further testimony how important future research and understanding of this illness is very important, for both the patient and their families as well as the health care system.

Imagine you are a practicing physician assistant working in an out-patient clinic and your first appointment involves a 66 year old professional man presenting with what he describes as "senior moments". He describes instances of misplacing items, forgetting appointments and noticing difficulties with his usual tasks at work for the past 2 years. Your next appointment is with a 71 year old woman with a 1 year history of memory loss, including difficulty retaining new information, word finding difficulties, as well as trouble recalling names of familiar faces. Are these concerns in keeping with the normal aging process or is this leaning into the domain of a neurocognitive disorder? What is on your differential diagnosis? How would you assess these patients in terms of their cognition and functioning? What would be your next steps if this turns out to be a Major NCD due to Alzheimer's Disease?

Looking at both of the patients above, it appears both have varying degrees of progressive cognitive decline primarily being memory loss. There are some beneficial tools online, including the 'warning signs' of Alzheimer's Disease for both patients and providers to consider when patients present with these symptoms (Table 1)[5]. These warning signs can be used as a general screening tool to help determine if further cognitive testing is warranted.

Table 1. 'Warning signs' of Alzheimer's disease[5]

1. Memory loss that affects daily function	6. Problems with abstract thinking (i.e. balancing a chequebook
2. Difficulty performing familiar tasks	7. Misplacing things like wallet or keys, perhaps in inappropriate places like an iron in the freezer
3. Problems with language (may forget simple words)	8. Changes in mood and behavior can be quite varied
4. Disorientation of time and place	9. Changes in personality - confused, suspicious, withdrawn
5. Poor or decreased judgment (not recognizing a medical problem needing attention)	10. Loss of initiative (passive, requiring cues and prompting to become involved)

Alzheimer's Disease

Alzheimer's disease (AD) is generally defined as an irreversible neurodegenerative disorder that is associated with progressive ageing and accumulation of misfolded protein aggregates in the brain. Large products of pathological amyloid-β and tau protein have been found in the form of plaques and neurofibrillary tangles in the brain, respectively.[6] These accumulations in the brain disrupt healthy tissue function and ultimately lead to cell death and subsequent volume loss. Imaging such as CT or MRI can visualize brain volume loss, which can be begin in the hippocampal regions of the temporal lobes (associated with memory and learning), then moves towards the frontal lobe (expressive language, executive function, personality) and occipital lobe (visuospatial processing and recognition)[6]. However, postmortem investigations are used to confirm diagnosis.

The brain changes in AD are a result of both genetic and environmental factors, including increased age; vascular risk factors such as diabetes, obesity, hypertension, hypercholesterolemia; social factors including low educational attainment and physical inactivity; as well as parental history of AD, especially at early-onset diagnosis[7]. Although the only way to confirm a diagnosis of AD is by postmortem evaluation of brain tissue, the diagnosis of probable AD, in addition to meeting the criteria for a neurocognitive disorder (see below), can be done by genetic testing or detailed clinical interview, involving some of the "warning signs" listed above. As well, other etiologies that may be presenting with similar clinical features to AD must be ruled out. Short-term memory problems are usually a cardinal and first sign for AD, however patients can develop dysfunction in other areas of functioning as well.

To educate ourselves on an illness such as Alzheimer's disease, it is important to broadly define the illness category it is classified under to further understand symptomatology. The neurocognitive disorders (NCDs) are a broad category in the Diagnostic and Statistical Manual of Mental Disorders, 5th ed[8] that involve disorders in which the primary clinical deficit is in cognitive function; a deficit that is acquired rather than developmental in nature. This means that the impaired cognition has not been present since birth or from an early age, but more of a functional decline from a previously achieved level. (To note, this broad category was previously referred to as 'dementia, delirium, amnestic and other cognitive disorders,' so although some of these terms are now considered outdated, dementia may still be used interchangeably in this paper as most previous studies used this terminology.) Neurocognitive disorders are then further broken down into delirium, major neurocognitive disorders, and mild neurocognitive disorders.

The diagnostic criteria for major neurocognitive disorders, previously referred to as dementia, include: (A) evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor or social cognition) based on: concern of the individual/informant/clinician and a substantial impairment in cognitive performance (typically 2 or more standard deviations below appropriate norms), preferably by standardized neuropsychological testing, (B) cognitive deficits interfering with independence in everyday activities, (C) deficits do not occur exclusively in context of delirium, and (D) cognitive deficits are not better explained by another mental disorder (Table 2a). Furthermore, these disorders can be specified based on presumed underlying etiology, for example, Alzheimer's disease, Lewy Body disease, Vascular disease, Parkinson's disease, and Traumatic Brain Injury. Further specifiers include whether there is a presence of a behavioral disturbance and their determined severity of cognitive decline (mild, moderate, severe). Mild neurocognitive disorders criteria follow the same guidelines, however, the cognitive decline is modest compared to significant and the deficits do not interfere with independence in everyday activities (Table 2b).

Specifically, and for the focus of this paper, major or mild neurocognitive disorder due to Alzheimer's disease (AD) has its own diagnostic criteria, including (A) meeting all criteria for major or mild NCD as listed above, (B) insidious onset and gradual progression of impairment in one or more cognitive domains, (C) level of diagnostic certainty of calling AD the "probable" or "possible" etiology of decline (i.e., evidence of a causative genetic mutation OR clear evidence of memory, learning and another cognitive domain decline, steady progressive decline in cognition without plateaus, and no evidence of mixed etiology). Lastly, (D) the disturbance is not better explained by another mental disorder, substances, or systemic disorder (Table 3).

Cognitive Assessment

Generally, to meet criteria A for major/mild NCD, one can use standardized cognitive testing to evaluate memory, thinking, problem-solving, and language abilities. The most commonly used assessment is the Mini Mental State Examination (MMSE), which consists of 11-12 questions (depending on version) and is used to assess orientation, registration, attention and calculation, recall, and language (Appendix 1)[9]. The maximum score is 30 points, with a score of 20 to 24 suggesting mild dementia, 13 to 20 suggesting moderate dementia, and less than 12 indicating severe dementia. Between 24 and 30, a patient may be considered to have “mild cognitive impairment” (MCI) or otherwise known as Mild Neurocognitive Disorder or pre-dementia although a diagnosis of dementia (Major NCD) cannot be

made as the decline in cognition is not significant enough to meet criteria[10]. The Montreal Cognitive Assessment (MoCA) is also scored out of 30, and has a larger focus on executive functioning[11]. It is important to be aware of the influence of formal education patients have received when using these tests.

Another frequently used cognitive assessment scale is the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) which is most commonly used to assess the efficacy of antidementia treatments[12]. This subscale is quite similar to the MMSE, in that it includes 11 tasks to assess cognitive domains of memory, language, orientation, and recall (Table 4). However, the scores for this test range from 0 to 70, and are backwards-compatible to the MMSE. In other words, a higher score (≥ 18) on this scale indicates *greater* cognitive impairment. This difference becomes important when examining treatment value because the anticipated outcome measures are reported in opposite directions (Table 5).

Management

Despite ongoing research around Alzheimer's disease, the range of treatments available to clinicians remains quite limited. There has been no consistent evidence to show benefit for any type of intervention to prevent the progression of cognitive decline in older adults. At this time, the goals of treatment in Alzheimer's disease aim to improve quality of life for patients and their caregivers, provide symptomatic management and to maintain optimal function[11]. Currently, there are only two main drug classes approved by the US FDA to help with stabilization of cognitive function: (1) cholinesterase inhibitors (ChEi) including donepezil, galantamine ER, and rivastigmine , as well as (2) the NMDA receptor antagonist, Memantine. Cholinesterase inhibitors are the most widely used class, and thus, will be the focus of this paper.

The mechanism of action of the cholinesterase inhibitors, sometimes referred to as "cognitive enhancers," function by increasing the levels of acetylcholine, a chemical neurotransmitter or "messenger" found in the body. Acetylcholine is involved with memory, judgment, and other thought processes[13]. Normally, certain brain cells are responsible for releasing acetylcholine to deliver messages to other cells. Once a message has been received, an enzyme called acetylcholinesterase breaks down the acetylcholine in the synapses between cells to be recycled. In patients with Alzheimer's disease, there is damage to the cells that produce and use acetylcholine, so the amount of acetylcholine available to carry messages is reduced. A cholinesterase inhibitor slows the breakdown of acetylcholine

by blocking the activity of acetylcholinesterase, which may help compensate for the loss of functioning brain cells. Unfortunately, these drugs cannot stop the underlying destruction of the nerve cells, so eventually, as brain damage progresses, the medications become less effective. They are currently licensed for mild to moderate AD, however, donepezil has also been approved for severe AD. Table 5 shows the individual pharmacokinetic profile of each of the medications separately[13].

Unfortunately this medication class comes with adverse events, common ones being nausea, vomiting and diarrhea. Many individuals experience these adverse events (NNH=12)[11], and incidence of events tends to increase with dose increases. Usually if a patient is otherwise healthy, adverse events should become tolerable for the patient over a few weeks if dosing is titrated slow and administered with food. Although rare, more serious side effects may include slowed heartbeat and syncope, increased stomach acid production with raised chances of bleeding ulcers, difficulty passing urine, seizures, and worsening lung problems if prior lung pathology present. As such, contraindications for prescribing the medications go along with these serious events: including uncontrolled severe asthma or COPD, bradycardia or cardiac conduction abnormalities (left bundle branch block), unexplained syncope, peptic ulcer disease, urinary obstruction, or seizure history. In addition, anticholinergic medications should be avoided as these will negate any benefits of ChEI's.[11,13]

Objective

The purpose of this paper is to analyze past research of the use of the cholinesterase inhibitors in patients with Alzheimer's disease to assess both the efficacy on cognitive function, as the fundamental symptom of AD, as well as the safety profile or adverse events associated with them.

Methods

A literature review was conducted by broadly searching for articles using PubMed and were restricted to free full text articles published in English between 2015 to 2020. Studies examined were meta-analyses and terms used in the search criteria included cholinesterase inhibitors effectiveness AND Alzheimer's. The search rendered 15 articles given the choice to use the most recent articles (written in the past 5 years), of which then underwent further abstract review to uncover their appropriateness for this study. Searches were specifically aimed to explore the use of cholinesterase inhibitors in Alzheimer's disease, therefore some articles were removed based on a broader focus on monotherapy vs. combo therapy with memantine, psychosocial interventions on cognitive function and post-stroke cognitive

impairment. Hence 4 articles remained that were deemed appropriate for the study, and reference lists of these articles were examined to look for any other relevant studies, to which 1 was added.

Results

Cognitive Function

When a healthcare professional is assessing efficacy of a treatment based on evidence from systematic research, it is important to note that it is ideal to compare treatments using randomized, double-blind trials. It is also critical to understand the way of interpreting a treatment's efficacy results when it is reported using a continuous measurement scale, such as the MMSE or ADAS-Cog. In these settings, a baseline score is calculated (i.e., assessment of cognitive function) and then the measurement is repeated post-treatment. The standardized mean difference (SMD) measure of effect adjusts for the treatment-versus-placebo (or sometimes, other treatment-versus- other treatment) differences for both the differing scales and size of population sample[14]. An SMD of zero means that the treatment and the "competitor" have equivalent effects. To assess any SMD value other than zero, it is important to first recognize if the outcome improvement is associated with higher or lower scores on the outcome measure. As an example, the MMSE uses higher scores to indicate greater cognitive function, and thus better efficacy (improvement from baseline) of the treatment. The SMDs greater than zero will then indicate the degree to which a treatment is more efficacious, while the SMDs less than zero suggest the degree to which treatment is less beneficial. Conversely, if a scale uses a lower score to indicate greater cognitive function (i.e., ADAS-Cog), then a SMD lower than zero indicates the degree of efficacy of a treatment. As general guidelines for magnitude, an SMD of (+/-) 0.2 is considered to have magnitude that is small, (+/-) 0.5 is medium, and (+/-) 0.8 is large[14]. These calculations are important to consider, as most of the meta-analyses in this paper included multiple cognitive assessment scales to assess cognition and medication effectiveness.

Tricco et al conducted a large analysis that involved 142 studies; 110 RCTs, 21 non-RCTs, and 11 cohort studies[15]. Separated by cognitive function scale, 56 RCTs (n=10446) used the MMSE and 53 RCTs (n=11348) used the ADAS-Cog. Examining the MMSE data, donepezil, the combination of donepezil and memantine, and rivastigmine patch were found statistically significant for showing cognitive improvement with medication use compared to placebo (SMD 1.39, 95% CrI; SMD 2.59, 95% CrI; SMD 2.02, 95%; respectively). As evaluated by the ADAS-Cog, donepezil and galantamine were suggested to show cognitive function improvement compared to placebo (SMD -3.29, 95% CrI; SMD -2.13, 95% CrI,

respectively). These results suggest some mild beneficial effect of cholinesterase inhibitors on cognition, however the amount of generalizability is questionable with the inclusion of some non-randomized controlled trials, as well as no reported minimum treatment duration inclusion criteria (ranged from only 2 weeks up to 260 weeks). Also, because many of the studies reported a dosage range only, the study was unable to properly examine and compare dosages to each other.

Another study by Fink et al. used both the MMSE and ADAS-Cog function tests, analyzing 55 studies of older patients with Alzheimer's disease who participated in pharmacotherapy for a minimum of twenty-four weeks[16]. Out of these studies, 25 compared cholinesterase inhibitors to placebo (n=9476), and 11 compared different dosages or formulations of the same cholinesterase inhibitor (n=5893). These trials mostly supported low strength evidence favoring "standard" dosing of cholinesterase inhibitors (donepezil 10mg/day; rivastigmine 12mg/day; or galantamine 32mg/day) over placebo for change in cognition and likelihood of improved cognition over 6 months. The average benefits versus placebo were small for mean change in cognitive test score (median pooled drug-specific SMD, 0.30 [range, 0.24 to 0.52], and ranged from no difference to small benefit for mean change in function (median pooled drug-specific SMD, 0.19 [range, -0.10 to 0.22]). Overall, there was slightly reduced short-term cognitive decline with the cholinesterase inhibitors but the differences versus placebo were not large enough to confidently report that they would have clinical importance.

Furthermore, Dou et al performed a network meta-analysis using 41 randomized controlled trials (RCTs) to compare and rank the efficacy of the cholinesterase inhibitors[17]. Efficacy in cognition was mainly evaluated by the ADAS-Cog, the MMSE, as well as the Severe Impairment Battery scale (usually used in moderate to severe AD). Participants were generally deemed as having mild to moderate AD if their baseline score was 10-26 and moderate-severe AD with scores of 0-15. Again, SMD was used to characterize the continuous results from the outcome scales. For those with mild to moderate AD, 22 trials were assessed using the ADAS-Cog scale and found that compared with placebo, galantamine 32mg daily (SMD -0.51), galantamine 24mg daily (SMD -0.50), and donepezil 10mg daily (SMD -0.40) were the most effective agents on cognition for mild to moderate AD (Fig. 1). For the 12 studies that examined moderate to severe AD, the SIB scale and MMSE were both used. It was found that donepezil 10mg daily combined with memantine 20mg was recommended for mod-severe AD (SMD 0.76), although the use of donepezil 10mg daily alone was still statistically significant to be efficacious (SMD 0.53).

Overall, these listed studies seem to consistently show evidence of mild improvement on cognitive function based on standard cognitive testing with the use of cholinesterase inhibitors. This statement was further supported by a large RCT meta-analysis (n=16106) by Blanco-Silvente et al., in which they concluded that the cholinesterase inhibitors were more efficacious than placebo for reducing cognitive symptoms (SMD=0.38, Fig. 2)[18]. Their findings also supported donepezil as the cholinesterase inhibitor of choice: better results on withdrawals for any reason and better efficacy on global symptomatology, but results would need to be further confirmed before developing clinical guidelines.

Birks and Harvey[19] looked specifically at the clinical use of donepezil in particular, in mild, moderate, and severe AD compared to placebo in addition to the efficacy of the different doses of donepezil (mostly 5mg/day or 10mg/day) using double-blind RCTs with treatment for at least 12 weeks or more. The main analysis used 13 studies (n=3396) to compare donepezil 10mg/day with placebo at 24 to 26 weeks of treatment (mean age=75). After 26 weeks of treatment, donepezil (compared with placebo) was associated with better outcomes for cognitive function using the ADAS-Cog (SMD -2.67, 95% CI), the MMSE score (SMD 1.05, 95% CI), and the SIB (SMD 5.92, 95% CI). The 10mg/day dose showed slightly better cognitive function outcomes on the ADAS-Cog (SMD -1.05, Fig. 3), but not statistically significant on the MMSE (SMD 0.15, Fig. 4) or SIB. These results support moderate-quality evidence that people with all stages of Alzheimer's disease treated between 12-24 weeks with donepezil show some small benefits in cognitive function.

Safety / Tolerability

When assessing whether or not a medical treatment is beneficial to give to patients, it is not just about the measured beneficial outcome but also whether or not the treatment has any risks or adverse events directly associated with it. In this case, the adverse events related to cholinesterase inhibitors previously documented can be mild such as nausea and diarrhea or more severe such as syncope or bradycardia[11,13]. These adverse events can involve withdrawal from the participated study or discontinuation of the treatment from any of the above or for perceived lack of efficacy.

All the studies assessed the safety profile of the cholinesterase inhibitors using an odds ratio (OR) calculation, which quantifies the strength of the association between two events. For the purposes of this paper, the ratio calculates the odds of adverse events in the presence of the cholinesterase inhibitors and the odds of adverse events occurring in the absence of them[14]. If the OR is equal to 1, it means there is no difference between using or not using the cholinesterase inhibitors. If the OR is

greater than 1, then these two events are considered to be associated (i.e., the presence of these medications raises the odds of adverse events), although this correlation does not imply causation. Confidence intervals (CI) can also be provided as a reference for reliability of the comparison.

Overall, the reviewed meta-analyses noted mild increase of adverse events with the cholinesterase inhibitors compared to the placebo group. Blanco-Silvente et al. looked at "all-cause discontinuation," which they defined as the proportion of randomized patients who did not complete the study for any reason, as well as discontinuation due to adverse events and perceived lack of efficacy[18]. They concluded that all-cause discontinuation was higher with the cholinesterase inhibitors than the placebo (OR=1.66, 95% CI) and discontinuation due to adverse events was also higher (OR=1.75, 95% CI). However, they found that discontinuation due to lack of efficacy was lower (OR=0.56, 95% CI). These results in combination with their documented modest improvement on cognition begs the question of whether or not the improvement compensates for the frequent adverse events and discontinuation rates, though they found a lower association of mortality with the treatment than the placebo (OR=0.65).

This study also compared the different medications to each other, showing rivastigmine as having a worse outcome than donepezil (diff OR= 1.66) but no statistically significant difference between donepezil and galantamine[18]. This somewhat coincides with Dou et al.,'s comparisons to placebo, who concluded that out of the cholinesterase inhibitors in their study, donepezil 5mg was the medication that did not present a significantly higher risk of adverse events[17], but reported that none of the active drugs were *more* tolerable for adverse events than the placebo for mild to moderate AD. They also included 10 studies assessing moderate to severe AD, and found that all drugs except for memantine 20mg (not a cholinesterase inhibitor) daily had a significantly higher risk of potentially adverse reactions than placebo (OR range 1.56-2.63). These reports together may indicate mild evidence to suggest donepezil may be the safest agent out of all options, but still quite inconclusive as there is significant heterogeneity between studies and donepezil still has adverse events associated with it as well.

When examining donepezil studies specifically, Birks and Harvey concluded that participants receiving donepezil were more likely to withdraw from studies before the end of treatment (24% vs. 20%, OR 1.25, 95% CI) or to experience an adverse event (72% vs. 65%, OR 1.59, 95% CI)[19]. Donepezil 10mg/day was associated with more adverse events and withdrawals from treatment than the 5mg/day

dosing but benefits on the 10mg/day dose were marginally larger than the 5mg/day dose, so the risk/benefit ratio of dosing remains unclear.

The rest of the studies remained inconsistent, as Tricco et al., concluded that no agent increased the risks of serious adverse events like falls or bradycardia, but most had some increased mild side effects associated like nausea and diarrhea.[15] Fink et al., however, suggested that the standard doses of donepezil and rivastigmine showed both mild increase of withdrawals due to adverse events and had some inconsistently increased serious adverse events.[16]

Discussion

The goal of this paper was to compile the most recent research regarding the use of cholinesterase inhibitors to assess their efficacy and tolerability in patients with Alzheimer's disease. To summarize, most of the articles that were explored showed mild to moderate evidence of improvement of overall cognitive function using cholinesterase inhibitors compared to placebo based on cognitive testing, including the ADAS-Cog and MMSE for mild to moderate Alzheimer's disease. In moderate to severe disease, it has been shown to be beneficial to add memantine, an NMDA antagonist, to the cholinesterase inhibitor treatment (more specifically, donepezil as it has been approved for severe AD), to improve cognitive function. When comparing dosing regimens of donepezil particularly, some studies suggest that there were benefits of higher dosing (10mg/day versus 5mg/day dosing), however, with that, increased likelihood of discontinuation of treatment and withdrawal from studies due to adverse events. The adverse events associated were usually mild- including nausea, vomiting, diarrhea, but still contributed to discontinuation of the medication and withdrawal from the associated study.

Limitations

The overarching limitation to almost all of the RCTs included in this paper was that the medications being studied were generally only used for 6 months or less, and a majority of analyses[15,17,18,19] used a mere 12 week minimum intervention period. This raises the concern of the ability to use these studies to infer any information about longer-term drug effects, which unfortunately, is an extremely important concern when discussing the risks/benefits ratio of a medication. In terms of efficacy, it becomes difficult to discern whether or not the improvements of cognitive function will last longer than the 6 month period, and when the progressive severity of the disease "takes over" the benefits of the medication. Furthermore, when assessing the tolerability or adverse events outcomes, it would be advantageous to be able to examine the "mild" adverse events as

discussed, to see if they still exist longer-term or if they tend to subside with time, and if any new adverse events develop in this time. There is a large gap in research in this area and should be a focus for the future.

In this literature review, the focus of the paper was specifically on cognitive function and tolerability or adverse events associated with the cholinesterase inhibitors. Although change in cognitive function is the most common symptom reported in patients with Alzheimer's disease, it is not the only symptom that patients may present with, therefore other outcomes need to be measured (i.e., neuropsychiatric symptoms like depressed mood, anxiety, sleep disturbances, irritability, as well as changes in activities of daily living, quality of life, institutionalization/relief of caregiver burden, etc.) to be able to better rationalize whether or not these medications are beneficial for the breadth of symptoms of this disease. A majority of the studies reported did include some of these types of outcome measures, in which they concluded that ChEIs have no evidence supporting efficacy on neuropsychiatric symptoms in patients, however, do improve overall global symptomatology[16,17,18]. The narrowness of this study's target outcomes is certainly a limitation that needs to be considered when trying to extend the risk/benefit ratio of this medication accurately.

Another limitation to be noted includes a majority of the known research compares these medications to placebo groups, but very few compare each medication to each other, which greatly limits the ability to help choose which medication is best to prescribe to patients, but merely points out that there is a benefit of medication use over nothing. Although this information is helpful, it doesn't allow for proper treatment guidelines to be made for healthcare providers to follow.

Finally, because there are a variety of different measurement scales for cognition function (i.e., ADAS-Cog, MMSE, and others), it makes it difficult to compare the study results of medication efficacy on cognition. Although these scales are similar on how they assess cognition, they are scored differently and unfortunately, in the opposite directions- meaning a negative SMD will be beneficial on one scale and disadvantageous to another as previously discussed. It is crucial to be extra vigilant when using these values and deciphering what they mean.

Recommendations

As a future healthcare provider, it is important to explain to patients that these medications have shown mild evidence of beneficial effects on cognition in patients with AD, however, the treatment is not disease modifiable and that the neurodegenerative process that is occurring will continue. It may

be helpful to explain to the patient, families, or caregivers the mechanism of action of these medications in clear, simple and understandable terms to further illustrate how they affect cognition. Patients and families should be given realistic goals, that lost functions will not be regained, but using these medications may slow the overall brain decline. The decision to use the medication should be made with individual considerations and goals in mind.

Non-adherence is one of the main factors for lack of effectiveness, and many patients/families have discontinued the medication prior to six months of treatment due to perceived lack of effect, side effects, poor knowledge/understanding, or depression. Compliance may be improved by ensuring better instructions and counselling are given, via telephone follow-ups, reminders, simplified dosing, and having other community supports available.

Conclusion

Overall, the studies gathered seem to support cholinesterase inhibitors showing mild benefits on cognitive function for patients with Alzheimer's disease, but the question remains on whether or not these positive effects overthrow the negative adverse events that have been inconsistently shown to be associated with them. Due to the heterogeneity of the studies examined, it appears the ability to make a firm suggestion on the use of cholinesterase inhibitors in patients with Alzheimer's disease remains quite difficult. To summarize, it appears that most of the studies could variably agree that the medication showed a somewhat poor risk-benefit relationship, as shown by the mild symptomatic improvement on cognitive function, but an overall increase in adverse events when compared to placebo.

This study only catches a glimpse of the effects of cholinesterase inhibitors, as it didn't discuss the other measurable outcomes besides cognitive function and tolerability, like neuropsychiatric symptoms, global impression change, rates of institutionalization and quality of life for example. While further research should continue to examine beneficial results and noticed side effects or adverse events, it would also seem important to ensure that long-term data could be investigated to see if these medications have benefit for extended periods. This type of data could be built into conversations with patients and families, when discussing the overall expectations of medication use. As the research doesn't appear to have a blatantly obvious answer on if the medications' benefits outweigh the risks, the use of them should be tailored directly towards the individualized patient and not to the Alzheimer's population as a whole.

Appendix 1. MMSE[9]

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Table 2. Neurocognitive Disorders (NCDs)[8]

(a) Major Neurocognitive Disorder	**(b) Mild Neurocognitive Disorder**
A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and 2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment	A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and 2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications)	B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required)
C. The cognitive deficits do not occur exclusively in the context of a delirium	C. The cognitive deficits do not occur exclusively in the context of delirium
D. The cognitive deficits are not better explained by another mental disorder (i.e., major depressive disorder, schizophrenia)	D. The cognitive deficits are not better explained by another mental disorder (i.e., major depressive disorder, schizophrenia)
Specify:	
1) **Whether due to -** Alzheimer's disease, Frontotemporal lobar degeneration, Lewy body disease, Vascular disease, Traumatic brain injury, Substance/medication misuse, HIV infection, Parkinson's disease, Huntington's disease, Another medical condition, multiple etiologies, unspecified	
2) **Without or with behavioral symptoms** (psychotic symptoms, mood disturbance, agitation, apathy)	
3) **Current severity -** mild (difficulties with instrumental activities of daily living like housework, managing money), moderate (difficulties with basic activities of daily living like feeding, dressing), or severe (fully dependent)	

Table 3. Major or Mild Neurocognitive Disorder due to Alzheimer's Disease[8]

NCD due to Alzheimer's Disease
A. Meets all criteria for major or mild neurocognitive disorder as above
B. Insidious onset and gradual progression of impairment in one or more cognitive domains
C. Level of diagnostic certainty of calling AD the "probable" or "possible" etiology of decline 1. *For major neurocognitive disorder:* a. **Probable AD** is diagnosed if either of the following is present; otherwise, **Possible AD** should be diagnosed. i. Evidence of causative Alzheimer's disease genetic mutation from family history or genetic testing ii. All three of the following are present: 1. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on history or testing) 2. Steadily progressive, gradual decline in cognition, without extended plateaus 3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline) 2. *For mild neurocognitive disorder:* a. **Probable AD** is diagnosed if there is evidence of causative AD genetic mutation from either genetic testing or family history b. **Possible AD** is diagnosed if there is no evidence of a causative AD genetic mutation from either genetic testing or family history, and all three of the following are present: i. Clear evidence of decline in memory and learning ii. Steadily progressive, gradual decline in cognition, without extended plateaus iii. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline)
D. Disturbance is not better explained by another mental disorder, substances, or systemic disorder

Table 4. Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) tasks[12]

Task	Description	Scoring
Word Recall	3 trials: List of 10 words read by the subject, then asked to verbally recall as many words as possible	Mean number of words not recalled [score = 0-10]
Naming Objects/Fingers	Name the fingers of their dominant hands and twelve objects: flower, bed, whistle, pencil, rattle, mask, scissors, comb, wallet, harmonica, stethoscope, and tongs.	The number of fingers and objects correctly named [score = 0-4]
Commands	Asked to perform commands that involve one to five steps. For example, the two-step command is to "Point to the ceiling, then to the floor."	Scored based on largest number of steps correctly performed, score of 0 = five step command correctly performed [score = 0-5]
Constructional Praxis	Shown four geometric forms (circle, two overlapping rectangles, rhombus, cube) and asked to copy them on a piece of paper.	Based on the number of correctly drawn forms [score = 0-5]
Ideational Praxis	Asked to pretend to send a letter to themselves: fold letter, put letter in envelope, seal envelope, address envelope, and put a stamp on the envelope.	Based on difficulty of performing the five components [score = 0-5]
Orientation	Asked the date, month, year, day of the week, season, time of day, place, and person.	The number of correct responses [score = 0-8]
Word Recognition	Read twelve words aloud, and then these twelve words are randomly shuffled with twelve new words, and the subject is asked whether they have previously seen each of the twenty-four words.	Mean number of correct responses across the 3 trials [score = 0-12]
Language	After the administration of the Word Recall task (Q1) 10 minutes of open-ended conversation occur between the test administrator & subject, before the remainder of the tasks are presented. These 10 minutes of conversation are used to assess language	Quality of speech is given a global rating by the administrator [scores = 0-5]
Comprehension of Spoken Language	This task also relies on the ten minutes of open-ended conversation. The administrator provides an assessment of how well the subject can understand speech.	The administrator provides a score [scores = 0-5]
Word Finding Difficulty	During open conversation, assessment of the level of difficulty the subject has in finding desired words.	The administer provides a score [scores = 0-5]
Remembering Test Instructions	Assessment of number of times that the subject needed to be reminded of instructions for the Word Recognition task	The administrator provides a score [scores = 0-5]

Table 5. Comparative Table of MMSE scale versus ADAS-Cog[9,12]

MMSE	ADAS-Cog
❑ Originally published by Folstein et al in 1975 ❑ Categories: orientation, registration, attention + calculation, recall, language, copying ❑ Total score = 30 ❑ Points are deducted for errors, therefore, the lower the score, the greater the cognitive impairment ❑ <24 signifies cognitive impairment	❑ Originally published in 1984 ❑ Categories: word recall, naming objects, commands, constructional praxis, ideational praxis, orientation, word recognition, language, spoken language comprehension, word finding difficulty, remembering instructions ❑ Total score = 0-70 ❑ Each error is given a point, so that, the greater the score, the greater the cognitive impairment ❑ >18 signifies cognitive impairment

Table 6. Pharmacokinetics of the Cholinesterase Inhibitors[13]

	Donepezil	Galantamine ER	Rivastigmine
Inhibition	Acetylcholinesterase		Acetylcholine +butyrylcholinesterase
Half-Life	70 hrs	7-8 hrs	3-4 hrs
Dose/Day	1		2
Starting Dose	5mg QAM	8mg QAM	1.5mg BID
Max Dose	10mg QAM	24mg QAM	6mg BID
CYP2D6/3A4 Metabolite	Yes		No
Elimination	Liver	Liver + Renal	Renal

Table 7. Summary of Study Backgrounds

	Study Objective	Inclusion Criteria	Data Selection	Studies (Participants)
Tricco et al[15]	- To examine effectiveness and safety of cognitive enhancers for AD	- No minimum tx length [range = 2-260 weeks]	- Medline, EMBASE, Cochrane Library, CINAHC, Ageline (inception to Mar 2016) for RCTs, quasi RCTs, and nonrandomized studies	- 142 studies; 110 RCTs, 21 non-RCTs, 11 cohort studies (n = 28,922)
Fink et al[16]	- To summarize evidence on effects of prescription drugs and supplements for *CATD treatment (tx) compared to placebo	- English - Minimum tx = 24 weeks - older adults w/ CATD that report dementia symptoms	- electronic bibliographic databases, ClinicalTrials.gov (inception to Nov 2019) - systemic review bibliographs	- 55 non-BPSD outcomes - 12 BPSD outcomes
Dou et al[17]	- To compare and rank efficacy and tolerability of cholinesterase inhibitors and memantine	- English - Minimum tx = 12 weeks [range 12-104 weeks, mean 28.7] - clinical diagnosis of AD	- Pubmed, Cochrane Central Register of Controlled Trials + EMBASE for RCTs (inception to July 2017)	- 41 RCTs (n = 18,898)
Blanco-Silvente et al[18]	- To examine the effect of ^AChEis on all-cause discontinuation, efficacy and safety for AD	- English - Minimum tx = 12 weeks	- Medline, Cochrane Central Register of Controlled Trials, psycINFO, ClinicalTrials.gov for double-blind RPCCTs (inception to Apr 2016)	- 43 RCTs (n = 16,106) [9555 (AChEis] versus 6551 (placebo)]
Birks & Harvey[19]	- To assess efficacy and safety of donepezil in mild, moderate, and severe AD; to compare efficacy and safety of different doses of donepezil	- English - Minimum tx = 12 weeks [most <6 months]	- Cochrane Dementia + Cognitive Improvement Specialized Register, Medline, EMBASE, PsycINFO (inception to May 2017)	- 28 double-blind RCTs (n = 8257)

*CATD= Clinical Alzheimer-type Dementia, ^AChEi = Acetylcholinesterase Inhibitors

Table 8. Summary of Study Results

	Cognitive Scales Used	Results	Limitations	Conclusions
Tricco et al[15]	- MMSE - ADAS-Cog	- Using MMSE; donepezil, donepezil + memantine, and rivastigmine patch sig. improved cognition - Using ADAS-Cog; donepezil and galantamine improved cognition - No agent increased risks of serious AEs but most had some increased risk for mild symptoms	- Use of nonrandomized trials - Not able to examine dosages, as many studies reported a dosage range only	- Generally, AChEIs have mild beneficial effect on cognition - Appear safe but generalizability to all populations is uncertain - Given more withdrawals in AChEi group, analysis could lead to bias favoring a positive outcome on cognition
Fink et al[16]	- MMSE - ADAS-Cog	- Across severity, low strength evidence that AChEis produce small ave. improvements in cognition over placebo - associated with increased withdrawal due to *AEs - in mod-severe AD, add on memantine inconsistently improved cognition	- Most drugs had few trials without high risk of bias	- AChEis slightly decrease short-term cognitive decline and reported functional decline but differences were of uncertain clinical importance
Dou et al[17]	- MMSE - ADAS-Cog - SIB	- Compared w/ placebo, galantamine 32mg and 24mg, and donepezil 10mg were most effective on cognition for mild-mod AD, donepezil 10mg AND memantine 20mg were recommended for mod-severe - None were likely to improve neuropsychiatric symptoms - All were less tolerable than placebo	- study heterogeneity may affect the results accuracy (large variation in treatment duration and differing scale use in mod-severe AD)	- Interventions have beneficial effects on cognition, function and global changes but not on neuropsychiatric symptoms - Choice of drug may depend on disease severity and symptoms
Blanco-Silvente et al[18]	- MMSE - ADAS-Cog	- All cause discontinuation and discontinuation due to adverse events were increased w/ AChEis - Improved cognitive function, global symptomatology, but not neuropsychiatric symptoms - Rivastigmine a/w poorer outcome on all-cause discontinuation - Mortality lower with AChEis	- Difficult to extrapolate to clinical practice - Length of trial was very short	- Poor risk-benefit relationship with AChEis, as indicated by mild symptomatic improvement and overall increase in all-cause discontinuation, but reduction in overall mortality rates with use
Birks & Harvey[19]	- MMSE - ADAS-Cog - SIB	- Donepezil showed better cognitive function outcomes using all scales, no difference on neuropsychiatric symptoms - more likely to withdraw from studies before treatment ended or to experience AE during study - Donepezil 5mg slightly worse cognitive function improvement on ADAS-Cog but fewer AE	- Minimal studies comparing donepezil dosing (3 studies)	- Moderate quality evidence of donepezil giving small benefits in cognitive function - Benefits slightly larger in 10mg dosing but AE and withdrawal rates increase with higher dosing

*AEs = adverse events

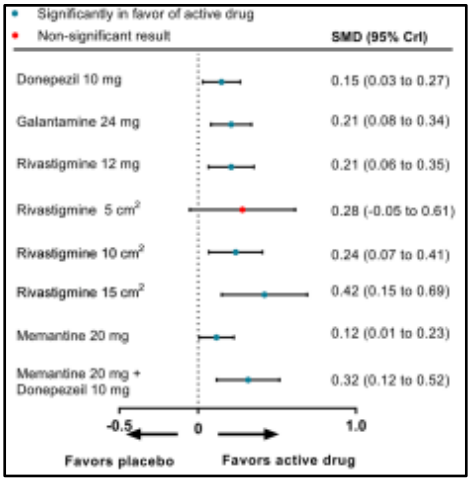

Fig 1. Forest plots of network meta-analysis of efficacy on cognitive function compared with placebo[17]

Outcome	n	Effect size (95% CI)	I^2 (%)
Discontinuation			
All-cause discontinuation	51	OR = 1.66 (1.30, 2.03)	51.7
Discontinuation due to AEs	44	OR = 1.75 (1.45, 2.05)	0
Discontinuation due to LoE	12	OR = 0.56 (0.34, 0.78)	0
Efficacy			
Cognitive function	41	SMD = 0.38 (0.28, 0.47)	41.1
Global change	32	SMD = 0.28 (0.22, 0.34)	0
Neuropsychiatric symptoms	19	SMD = 0.03 (-0.04, 0.09)	0
Functional capacity	18	SMD = 0.16 (0.11, 0.20)	0
Safety			
Mortality	19	OR = 0. 65 (0.47, 0.83)	0
Proportion patients AEs	34	OR = 1.69 (1.46, 1.93)	0
Proportion patients SAEs	32	OR = 1.10 (0.84, 1.35)	0

Abbreviations: AE, adverse event; LoE, Lack of efficacy; OR, odds ratio.

Fig 2. Effect of Cholinesterase Inhibitors on Discontinuation, Efficacy and Safety Outcomes in Patients with AD[18]

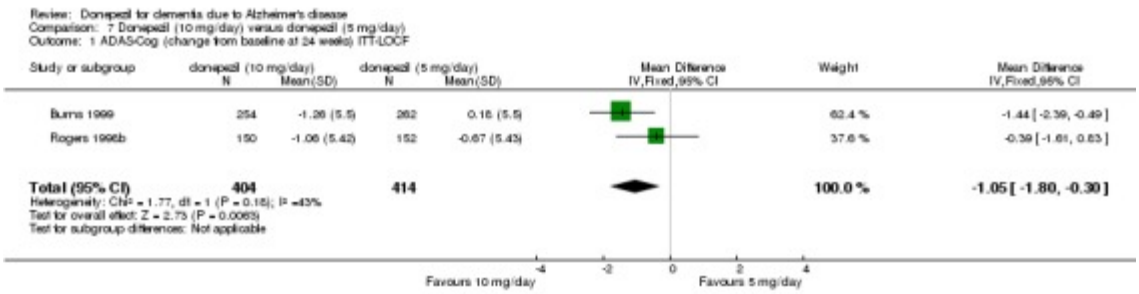

Fig 3. Donepezil 10mg/day versus donepezil 5mg/day using ADAS-Cog[19]

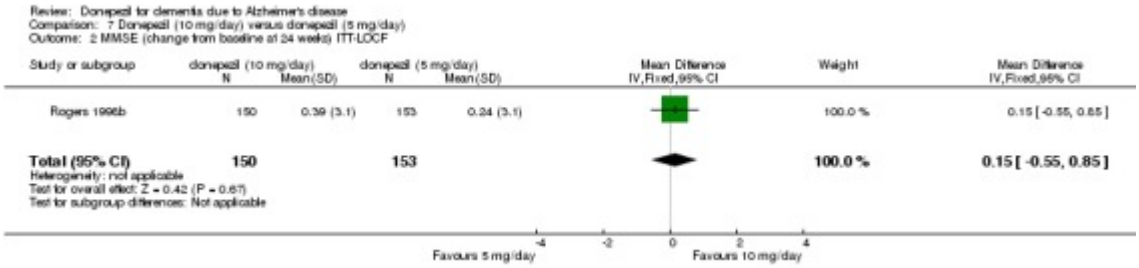

Fig 4. Donepezil 10mg/day versus donepezil 5mg/day using MMSE score[19]

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