This literature review will discuss the effects of aniracetam and oxiracetam on patients afflicted with Alzheimer’s disease. Alzheimer’s disease is an irreversible and progressive disease. Symptoms of the disease include deterioration in memory, dysfunctional daily living, changes in mood and personality, confusion, impaired communication, and loss of bowel and bladder control (National Institutes of Health (NIH), n.d.).

Alzheimer’s disease is caused by a combination of genetic and environmental factors (Gatz, 2006). Typical onset of Alzheimer’s disease is above the age of 60 years. A definite diagnosis of Alzheimer’s disease cannot be determined until an autopsy is performed. Due to the need for an autopsy to be performed, individuals may be diagnosed with possible Alzheimer’s disease through questionnaires, memory diagnostics, blood tests, urinalyses, and brain imaging. (NIH, n.d.).

Current approaches to treating Alzheimer’s disease focus on drug therapy (NIH, n.d.). The purpose of using drugs is to slow down or delay the onset of symptoms in those afflicted with Alzheimer’s disease (NIH, n.d.). The use of aniracetam and oxiracetam in treating Alzheimer’s disease was researched heavily in the 1990s (Bottini, Vallar, Cappa, Monza, Scarpini, Baron, & Scarrato, 1992; Dager, Loebel, Claypool, Case, Budech, & Dunner, 1992; Davis, Thal, Gamzu, Davis, Woolson, Gracon, & Doody, 1992; Gouliaev, & Senning, 1994). These studies have shown that the Racetam compounds decrease symptoms of Alzheimer’s disease. However, the research and clinical use of oxiracetam and aniracetam has come to a standstill for unknown reasons (Kenda & Matagne, 2012).

Past studies have looked into how these drugs interact with the brain. Oxiracetam and aniracetam work in similar ways: oxiracetam stimulates acetylcholine utilization in the hippocampus and indirectly stimulates AMPA glutamate receptors (Gouliaev and Senning, 1994). Aniracetam, on the other hand, enhances the efficacy of AMPA-induced calcium influx, increases acetylcholine content in the hippocampus and cerebral cortex, and decreases the dopamine level in the striatum and the hypothalamus. An important characteris-
tic of these Racetam compounds relates to their effect on acetylcholine in the hippocampus. Acetylcholine in the hippocampus has been associated with learning activation and memory; animal models with induced memory impairments have found behavioral deficits in learning, as well as a decrease in hippocampal acetylcholine (Roland, 2003).

Currently, relatively newer and more popular medications, such as donepezil and tacrine, have been discovered and are now first-line treatments for Alzheimer's disease. Whether these new medications are more effective than Racetam compounds is an issue that must be addressed. This literature review will explore Racetam research that is focused on certain aspects of the disease (cognitive ability, and quality of life), including a comparison between Racetam containing drugs and recent medications, in terms of their therapeutic efficacy.

The Racetam Compounds

Oxiracetam

Oxiracetam, like other Racetam compounds, is not currently prescribed as a treatment for Alzheimer’s disease. However, studies suggest that oxiracetam has the ability to slow down, or completely halt, the disease’s progression. There are a number of studies that have shown an improvement in patients’ symptoms pertaining to cognitive ability. In a double-blind, between-patient study conducted by Bottini et al. (1992), the administration of 1600 mg/day of oxiracetam was observed to significantly improve phonemic memory, semantic memory, short-term memory recall, and recognition in Alzheimer’s disease patients. In contrast, a steady deterioration in cognitive ability, according to results found from the same group of neuropsychological tests, was observed in the placebo condition. Most noteworthy were the results of the semantic memory tests (including short story recall, semantic tasks, digit span tests, and word list tests), which showed significant improvements in the oxiracetam group. A major weakness of Bottini et al.’s (1992) study was its small sample size of 65 participants. Nonetheless, a study by Maina, Fiori, Torta, Fagiani, Ravizza, Bonavita, and Maccioli (2008), found similar results using a larger sample size of 289 participants. In particular, the oxiracetam group showed significant improvement on the Blessed Dementia Scale (BDS); the BDS contains scales that measure information, memory, and concentration abilities, all of which are indicators of cognitive improvement. In a study by Villardita, Grioli, Lomeo and Cattaneo’s (1992), similar results in cognitive improvement were found, where cognitive ability was operationalized as memory retention, and was tested using word recall and word recognition.

Other studies, however, have brought the efficacy of oxiracetam on cognitive ability into question. For example, a study by Green, Goldstein, Auchus, Presley, Clark, Van Tuyl, and Karp (1992) found no therapeutic efficacy of the oxiracetam treatment on Alzheimer’s disease. This study, however, had a number of flaws: a small sample size of 24 participants; withdrawal of participant results; plausible bias (funded by GSK pharmaceuticals); and premature termination after one month, instead of the planned three months. Despite its shortcomings, the study concluded that oxiracetam did not offer meaningful clinical improvement in cognitive functioning. It is important to note that studies where researchers found significant positive results were performed over a minimum period of 12 weeks (Bottini et al. 1992; Maina, et al., 1989; Villardita et al., 1992). Thus, the research suggests that oxiracetam requires at least 12 weeks to demonstrate observable positive effects on participants afflicted with Alzheimer’s disease. After a thorough review of the oxiracetam literature, only one methodologically imperfect study was found (see Green et al., 1992). Evidence found in the majority of articles suggests that oxiracetam may be effective in improving the cognitive functioning of participants with Alzheimer's disease (Bottini, et al., 1992; Dager, et al., 1992; Maina, et al., 1989).

Quality of life was another factor that was seen
Aniracetam

There have been a small number of studies conducted on the use of aniracetam in the treatment of Alzheimer's disease. One such study was a double-blind placebo study conducted by Senin, Abate, Fieschi & Gori (1991). In this particular study, researchers looked at the Rey-15 word test as a measure of memory feigning, the Corsi test as an assessment of visuo-spatial short term working memory, and the Raven colored progressive matrices as a measure of abstract reasoning. Some other factors examined in this same study were executive attention, as measured by the Gibson spiral maze, and selective attention, as measured by the Toulouse-Pieron test. Scores on these psychometric tests of cognitive ability all showed an improvement in the aniracetam-treated group, whereas the results showed cognitive deterioration (a common symptom of Alzheimer's disease) in the placebo group. The reason for this deterioration is likely due to the fact that patients in the placebo group were not given Alzheimer's medication and the disease symptoms progressed. This study is important because it was conducted with a large study sample of 109 patients over a long period of time (~6 months). A large study sample is crucial in order to observe whether the drug's effect on a patient group truly made a difference; a small sample size will not be able representative of the effects on a large group such as a community or province. Ensuring drug trials monitor patients over a long period of time is crucial. In this way, researchers can observe the true effects of the drug on a patient group as time goes on, not just the acute effects of a medication that may not last. The most resonating result in this study was the improve-
ment of test scores pertaining to short-term memory recall, attention ability, and general intelligence/reasoning to above pre-treatment levels in aniracetam-treated patients. Since Alzheimer’s disease causes deterioration in cognitive abilities (NIH, n.d.), these results suggest the possibility of aniracetam reversing the cognitive effects of this disease. Further research on this drug may be able to provide additional evidence in support of this hypothesis. Similar to the other Racetam compounds, the most common adverse side effects in the administration of aniracetam were gastrointestinal symptoms (diarrhea, nausea, etc.). However, these symptoms were only observed in 7% of the aniracetam patients (Senin et al., 1991). These studies suggest that, overall, aniracetam is well tolerated, and relatively safe for use in patients (Senin et al., 1991; Gouliaev & Senning, 1994).

**Currently Popular Medications**

**Donepezil**

Donepezil (Aricept) is a common medication prescribed to Alzheimer’s disease patients. Although its therapeutic advantages have been observed in the treatment of Alzheimer’s disease, not all patients respond to donepezil. In one study, donepezil was found to be effective in increasing Mini-Mental State Examination scores (a test of cognitive impairment used to screen for dementia) on 69% of patients, while the remaining 31% of patients showed uncertain improvements (Johannsen, Salmon, Hampel, Xu, Richardson, Qvitzau, & Schindler, 2006). In this double-blind, placebo-controlled study, the authors found that at 12 weeks of treatment with donepezil, there were no significant differences in cognitive test scores between the placebo and donepezil group, as indicated by the Mini-Mental State Examination (Johannsen, et al., 2006). However, after more than 12 weeks of treatment with donepezil, improvements in patients’ cognition were observed when measured by the Alzheimer’s Disease Assessment Scale, a cognitive subscale (ADAS). These improvements were operationalized as a smaller decline in cognitive functioning relative to the placebo group (Johannsen et al., 2006). Although this study demonstrated donepezil’s ability to slow down the deterioration of cognitive ability, it failed to demonstrate its ability to halt or improve the cognitive ability of individuals afflicted with Alzheimer’s disease beyond baseline. Interestingly, patients’ physicians acknowledged an improvement in their patients’ behaviour and cognitive functioning. However, this acknowledgment of improvement was also noticed when patients’ cognitive scores were declining (Johannsen et al., 2006). Consequently, the physicians’ acknowledgement might indicate a lack of scale accuracy or a bias on their part, perhaps due to their prior knowledge of donepezil’s proposed effects. In Johannsen et al.’s (2006) study, the authors found donepezil to be well tolerated. There was a low frequency of adverse side effects, though no statistical test was conducted to support this data. The majority of these side effects were mild to moderate and affected the digestive or nervous systems. In general, donepezil does not appear to pose a safety or tolerability risk to patients.

**Tacrine**

In a double-blind, placebo-controlled study by Davis et al. (1992), it was found that treatment with tacrine in Alzheimer’s disease patients resulted in a significant decrease in the decline of cognitive function, as measured by the ADAS. Davis et al. (1992) reported no tolerability or safety issues. Similar to donepezil, tacrine did not halt or improve the condition of the disease; rather, it appeared to slow down the inevitable deterioration of cognitive functioning that is symptomatic in Alzheimer’s disease.

Using the Instrumental Activities of Daily Living scale (IADL), Knopman, Schneider, Davis, Talwalker, Smith, Hoover, and Gracon (1996) found that tacrine treatment improved daily living in patients treated with tacrine compared to the placebo group. However, this increase in IADL score was not significant. As noted from previous studies conducted to assess Alzheimer’s medications (Johannsen et al., 2006), it is possible that
the effect of tacrine slowing cognitive deterioration may have concurrently slowed the negative effects of Alzheimer’s disease on participants’ quality of life. The literature suggests that tacrine treatment does not influence improvement in cognitive abilities and quality of life in patients with Alzheimer’s disease, but is useful in slowing down the cognitive deterioration caused by the disease.

**Discussion**

**Cognitive Deterioration**

The deterioration of cognitive ability is one of the main symptoms of Alzheimer’s disease. It appears that current medications (i.e., donepezil and tacrine) slow the deterioration of cognitive abilities while aniracetam and oxiracetam appear to improve cognitive abilities above baseline. Studies conducted with aniracetam demonstrate the drug’s ability to reverse the cognitive deterioration caused by Alzheimer’s disease (Senin, et al., 1991). Oxiracetam appears to have the most substantiating evidence in favour of its ability to reverse the effects of Alzheimer’s disease. It not only halts the progression of Alzheimer’s disease, but also improves the patient’s cognitive abilities (Senin, et al., 1991). The literature suggests that these improvements in cognitive ability mostly pertain to memory ability (i.e., semantic, recognition, short term, and associative memory), attention, abstract reasoning, executive functioning, and concentration (Bottini et al., 1992; Maina, et al., 1989; Senin, Abate, Fieschi, and Gori, 1991; Vellardita et al., 1992). Thus, evidence suggests that Racetam compounds are equally, or more, efficacious in the treatment of Alzheimer’s disease in comparison to the current medications used.

**Future Research**

Despite oxiracetam and aniracetam’s relatively superior therapeutic effects on patients, no study comparing the therapeutic efficacies of Racetams to those of donepezil and tacrine have been conducted. If these promising results lead to further research, however, Racetam medications could be offered as clinical treatment options, and patients could have access to an inexpensive compound more efficacious in the treatment of Alzheimer’s disease than the currently used medications. In order to counter the weaknesses of previous studies, future research on these reviewed medications (donepezil, tacrine, and the Racetam compounds) should use larger sample sizes, observe the drug effects over a longer period of time, and compare the effects of different medications directly against each other using a single study design. Studies of high methodological quality -- having those characteristics of which were described above, including a large sample size — replicated multiple times, are needed to wade out any positive results that may occur due to chance. Also, given that these studies are dated (Bottini, et al., 1992; Maina, et al., 1989; Dager, et al., 1992; Davis, et al., 1992; Gouliaev & Senning, 1994; Green, et al., 1992; Knoiman, et al., 1996; Senin, et al., 1991), newer, more validated, and reliable neuropsychological tests should be administered concurrently with the administration of oxiracetam and aniracetam to better assess their effects.

Oxiracetam and aniracetam are currently sold at $649 USD and $329 US per kg, respectively (Cerebral-Health, n.d.). At the doses used in the cited studies of 1600mg/day and 1500mg/day, the price of oxiracetam and aniracetam administration per day would be $1.04 USD and $0.49 USD, respectively. These prices contrast with Aricept at $8.03 USD, and tacrine at $8.03 USD, per day (DrugBank, 2011). Despite the lack of research surrounding differences in these medications, it is apparent that the Racetam compounds are much cheaper than the other drugs discussed in this paper. As previously stated, no studies have compared the Racetam drugs with donepezil or tacrine, and consequently, direct comparisons of drug efficacy are difficult. When considering the large price difference in these drugs, common sense would suggest that the more expensive compound be more efficacious in reducing Alzheimer symptoms. However, this literature review did not find
that the more expensive medication was more effective. As discussed, the Racetam compounds appear to provide a greater benefit to the patients in the studies discussed in this paper (Bottini et al., 1992; Maina et al., 1989; Senin, Abate, Fieschi, and Gori, 1991; Villardita et al., 1992) than either donepezil or tacrine (Johannsen et al., 2006; Knopman et al., 1996).

**Conclusion**

Racetam compounds have shown promise in the treatment of Alzheimer’s disease. They are well tolerated by patients and exhibit significant therapeutic efficacy. In comparison to current medications, studies suggest that Racetam compounds are either equally, if not more, effective in inducing improvements in cognitive ability and quality of life. These compounds are an inexpensive alternative to current medications. Despite showing positive results in the use of Alzheimer’s disease and dementia, Racetam research is lacking. Prescribing Racetam compounds may cause the reversal or retardation of some of the symptoms of the disease seen in patients. Thus, future research on Alzheimer’s disease and other forms of dementia should also focus on Racetam compounds, to assess whether the effects of previous treatments were valid or due to chance.

**References**


