A Comparative study of piracetam, donepezil and captopril on short- and long-term memory in mice

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ABSTRACT

Background: Nootropics are primarily used in the management of cognitive impairments, improvement of mental alertness, as well as boosting of energy levels in clinical patients. They are also used casually by healthy individuals to improve performance and gain competitive edge on certain cognitive-demanding tasks.

Objective: The study examined the effect of some selected nootropics on short term memory (STM), and long term memory (LTM) with the aim of comparing their effectiveness.

Methods: Animals used in the study comprised of Swiss albino mice weighing between 20-25 g, which were randomly shared into four treatment groups (Normal Saline, Piracetam, Captopril and Donepezil) and treated accordingly. The memory enhancing activity of each drug was tested using the Barnes maze model.

Results: The result on short-term memory evaluation reveal that donepezil produced a significant memory retention effect compared with captopril ($p<0.05$). The results also show that there was no significant difference in the performance recorded between donepezil and piracetam ($p>0.05$) on memory retention. The results further show that donepezil produced a significant improvement in long-term memory than both piracetam and captopril ($p<0.05$).

Conclusion: This study was able to establish that the memory enhancing effect of donepezil is significantly higher than those of piracetam and captopril. This pharmacological effect may be partly attributed to the longer half-life it possesses compared to piracetam and captopril.

Keywords: Memory, nootropics, donepezil, piracetam, captopril, barnes maze

Une étude comparative du piracétam, du donépézil et du captopril sur la mémoire à court et à long terme chez la souris

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RÉSUMÉ

Contexte : Les nootropiques sont principalement utilisés dans la gestion des déficiences cognitives, l'amélioration de la vigilance mentale, ainsi que l'augmentation des niveaux d'énergie chez les patients cliniques. Ils sont également utilisés occasionnellement par des personnes en bonne santé pour améliorer leurs performances et obtenir un avantage concurrentiel sur certaines tâches exigeantes sur le plan cognitif.

Objectif : L'étude a examiné l'effet de certains nootropiques sélectionnés sur la mémoire à court terme (MCT) et la mémoire à long terme (MLT) dans le but de comparer leur efficacité.

Méthode : Les animaux utilisés dans l'étude comprenaient des souris albinos suisses pesant entre 20 et 25 g, qui ont été réparties au hasard en quatre groupes de traitement (solution saline normale, piracétam, captopril et donépézil) et traitées en conséquence. L'activité d'amélioration de la mémoire de chaque médicament a été testée à l'aide du modèle de labyrinthe de Barnes.

Résultats : Les résultats de l'évaluation de la mémoire à court terme révèlent que le donépézil a produit un effet significatif de rétention de la mémoire par rapport au captopril ($p<0,05$). Les résultats montrent également qu'il n'y avait pas de différence significative dans les performances enregistrées entre le donépézil et le piracétam ($p>0,05$) sur la rétention de la mémoire. Les résultats montrent en outre que le donépézil a produit une amélioration significative de la mémoire à long terme par rapport au piracétam et au captopril ($p<0,05$).

Conclusion : Cette étude a permis d'établir que l'effet du donépézil sur l'amélioration de la mémoire est significativement plus élevé que ceux du piracétam et du captopril. Cet effet pharmacologique peut être partiellement attribué à la demi-vie plus longue qu'il possède par rapport au piracétam et au captopril.

Mots clés : Mémoire, nootropiques, donépézil, piracétam, captopril, labyrinthe de Barnes

INTRODUCTION

From time past, the human memory has been considered synonymous to a computer.[1] Memory is a vital faculty of humans that is indispensable and has become the basis for relating with the environment. In the absence of memory, human will be limited in terms of reflections on past and future events and understanding present operations.[2,3] Matlin[4] defined memory as the process of maintaining information over a period of time. It is regarded as a means by which 'we draw on our past experiences in order to use this information in the present.'[2] The term memory encompasses three important aspects of information processing, namely; sensory, short-term memory, and long-term memory.[5] The sensory memory is a system of short-acting memory that processes information received by the receptors of the sense organs.[6] These information are further selected to be transferred into short-term memory with the goal of future recall. The short-term memory (STM) is a storage system which can only accomodate a small amount of information within a limited amount of time, usually less than a minute.[7] These information becomes available to be processed in order to become useful for modification, interpretation, and storage. This process becomes achievable as a result of a special type of memory called 'working memory.'[8] According to cognitive psychologists like George Miller,[9] the STM can hold between 5 and 9 units of information. Additionally, duration of working memory is limited to 2 to 18 seconds. This was confirmed through the work of Brown[10] and Peterson and Peterson[11] (now called Brown-Peterson paradigm). Their findings show that, information that is not rehearsed (practiced) dissipates from the working memory in about 18 seconds. As a result of these limitations (limited space and short duration), as new items enter, older ones are pushed out. However, with practice and new skills, the limitations can be overcome.[12]

Although it is useful to hold information in sensory and short-term memory, humans also rely on the long-term memory (LTM). The information processing model posits that long-term memory is a system that encodes, stores, and retrieves information. Unless information is encoded, it cannot be stored and retrieved/remembered.[12] The dual-store memory model proposed by Atkinson & Shiffrin in 1968 further explains the operations of the long-term memory in relation to the short-term memory. According to the model, the capacity and duration of the short-term memory can be increased through rehearsal[12] and the longer an item or information stays in the short-term memory, the stronger its association in long-term memory.[5]

The study is interested in examining and comparing the effect of some selected nootropics on short-term memory and long-term memory. The act of memory enhancement using pharmaceutical products has received considerable medical and public attention[13,14] and has likewise remained a trending topic in both scholarly and public debate.[15] Neuroenhancers, otherwise called nootropics, are a group of heterogeneous drugs with psychotropic properties which produce selective facilitatory effect on integrative functions of the Central Nervous System primarily on intellectual performance, learning capability and memory.[16,17] Nootropics are commonly used medically to treat a variety of neurodegenerative disorders associated with loss of memory and other disturbances of cortical functions such as are found in Alzheimer's disease.

While nootropics are primarily used in the management of medical disorders including Alzheimer's disease, they are sometimes used by healthy individuals to improve performance, increase efficiency and gain competitive edge on certain cognitive-demanding tasks. For instance, some students make use of nootropics to improve their concentration at school and help them study efficiently.[18] Nootropics are known to exert their pharmacological effects via multiple chains of actions on the Central Nervous System[16] with the goal of improving cognition; hence they are also called 'cognitive (memory) enhancers.'[19]

A few drugs such as caffeine,[20] nicotine[21] and amphetamine[22] have been reported to possess nootropic activities; however the scope of the present study only covers piracetam (an example of racetams), donepezil (an example of cholinesterase inhibitors) and captopril (an example of angiotensin-converting enzyme inhibitors) as our test drugs.

Piracetam (known as nootropyl), is one of the most popular nootropics. It is a synthetic compound belonging to the family of racetam.[23] Piracetam was first synthesized in 1964 by UCB Pharma in Belgium,[23,24] making it the first of the racetam family to be discovered. It has been used successfully in the treatment of several pathological and experimentally-induced conditions in both humans and animal models.[25,26] Piracetam has been used to enhance verbal learning and

comprehension in dyslexic children.[27,28,29] Tallal *et al.*[28] were able to demonstrate in their double-blind, placebo controlled study that piracetam significantly improved effective reading and writing ability, including speed and accuracy in fifty-five dyslexic boys, aged 8-13 years over a period of 12 weeks. Piracetam has also been shown to improve cognitive function in patients suffering from age-associated memory impairment[30,31] and decreased cognitive function associated with coronary bypass surgery.[32,33] Piracetam has additionally demonstrated viability in reversing hypoxia-induced amnesia and learning difficulties[34] and in potentiating the anticonvulsant action of valproate in myoclonus epilepsy.[35]

Donepezil is the first line palliative treatment for Alzheimer's disorder.[36] The drug acts by inhibiting the cholinesterase enzyme responsible for degrading acetylcholine neurotransmitters at cholinergic synapses, consequently facilitating neurotransmission. Nootropic potentials of donepezil have been established in several studies.[37,38,39,40] For example, Winblad *et al.*[40] carried out a one-year randomized, placebo-controlled study examining the long-term clinical efficacy and safety of donepezil in patients suffering from mild to moderate Alzheimer's disease. The results of their study revealed that donepezil produced improved cognition, global assessment and activities of daily living over placebo. Donepezil has consistently demonstrated modest improvements in cognitive function in these studies, despite the less promising use of anticholinesterase inhibitors in clinical use.

Captopril belongs to a drug class known as angiotensin-converting enzyme inhibitors which are originally known for their clinical use in the management of hypertension. Additionally, studies have shown that they also exert centrally mediated actions. For example, two different studies conducted by Mondadori and Etienne[41] and Raghavendra *et al.*[42] reported that captopril and enalapril have been shown to remarkably improve learning and memory processes in mice. HOE288, which is also in the family of angiotensin-converting enzyme inhibitors, has been reported to improve memory by reversing scopolamine-induced amnesia in mice and rats.[43]

Despite the fact that the nootropic activity of these drugs is known for years in several behavioural studies, comparative studies on their level of effectiveness is scarce. In fact, few studies that have been carried out used different groups of nootropic drugs.[42,44,45] Vasil'eva *et al.*[44] carried out a study on the effects of nootropic drugs such as piracetam, fenotropil, noopept, semax and fenotropil on exploratory behaviour, locomotor activity and anxiety levels of two different strains of mice. To the best of our knowledge and within available resources, no studies have compared nootropic drugs in Nigeria, particularly with the strains of mice bred in Nigeria. In the light of above, the present study compared the cognitive-enhancing properties of some nootropic drugs in healthy mice using the Barnes maze paradigm. The study compared the effects of these drugs on short-term memory and long-term memory.

MATERIALS AND METHODS

Animals

The Swiss albino mice used for the study were obtained from the Animal House Unit of the College of Medicine, University of Lagos; Idiaraba, Nigeria. The mice were housed in a room with alternating light and dark cycle of 12 hours each and they had free access to food and water. The animals were left to acclimatize to their new environment for 48 hours before the commencement of the research. The nature of the study was experimental, involving a two-phase study. The first phase involved 20 healthy male albino mice trained in a Barnes maze for 4 days in 4 training trials per day. Twenty Swiss albino mice (male, aged 12-14 weeks), weighing between 20-25 g, were randomly selected into four treatment groups. The experiment was carried out after going through an ethical evaluation process by the Research and Ethics Committee, College of Medicine of the University of Lagos (CMUL/HREC/04/17/120). The Animal care and handling was conducted in compliance with the National Regulations for Animal Research.[46]

Drugs

The drugs used in this study were obtained from the following drug houses. Piracetam (Nootropil®, Star Pharmaceutical Ltd. Qionghai, China), donezepil (Torrent Pharma Ltd., U.K.), captopril (Bristol Laboratories Ltd., U.K.) and normal saline (Unique Pharmaceuticals Ltd., Nigeria). Review of literatures was the basis for dose selection; 200 mg/kg for piracetam,[47] 10 mg/kg for captopril 42 and 0.5 mg/kg for donepezil hydrochloride.[48] Piracetam, captopril and donepezil were dissolved separately in normal saline and injected intraperitoneally (i.p.). Volume of i.p. injection was 1 ml/100 g of mouse.[49]

Barnes maze apparatus

Barnes maze (BM) is one of the models of behavioural studies frequently used to evaluate spatial learning and memory because it is considered less aversive and allows testing under less distressing conditions without physical exertion[50,51] BM is a dry-land maze consisting of an elevated circular platform of about 92 cm in diameter with 20 holes (diameter of holes: 5 cm) placed 2 cm from the edge and equally distributed around the surface. The platform was elevated by 105 cm from the floor of the room (where the experiment took place) and was marked into four equal quadrants. The escape box was made of plastic (28 cm × 22 cm × 21 cm).[52] A light stand with two 150-watt flood lamps was held 155 cm above the maze platform to provide aversive stimulus.[53] With the Barnes maze, the animals were motivated by the bright lights and scary open surface to locate an escape hole to a dark chamber located beneath the platform called target box.

Procedure

The procedure was divided into three phases; pre-training phase, acquisition phase and the probe phase. In the pre-training phase, each mouse was placed in the middle of the maze in a black-coloured cylindrical start chamber (10.5 cm), and the bright light was turned on. After 10 seconds, the chamber was lifted, and the mouse was pre-trained to enter the target hole (hole that contained the escape box) by guiding it with what to the box and allowing it to remain there for 2 minutes. Following the pre-training phase, the acquisition phase (training phase) started. At the beginning of each trial in this phase, each mouse was placed in the same start chamber for 10 seconds and thereafter the light was turned on. The chamber was lifted and the mouse was allowed to freely explore the maze. A trial ends when the mouse is able to locate and enter the escape box or after 3 minutes. Immediately after the mouse entered the escape box, the lights were turned off and the mouse was allowed to stay in the box for 1 minute before returning to home cage. Each mouse was exposed to four trials per day for 4 days (D1-D4) with inter-trial interval of 15 min. The maze surface was cleaned with 70% alcohol solution and rotated by 180 degree after each trial in order to eliminate the possibility of the use of olfactory and intra-maze cues respectively by mice.[54] Trials were recorded using a video camcorder (Canon® HD CMOS PRO) mounted at a fixed position to record all activities on the maze.

Evaluation of short-term memory (STM)

Following the acquisition (training) phase, the probe phase began on the 5th day (D5). Each mouse received a probe trial for 90 seconds to check the short-retention memory. During the trial, the hole leading to the escape box was closed and mice were allowed to freely explore the maze before returning to home cage. The latency (LT; time taken by each mouse to reach the target hole for the first time) and the time spent in target quadrant (TSTQ; time spent in the quadrant that contained the target hole) were recorded for each treatment group.

Evaluation of long-term memory (LTM)

In examining this protocol, mice did not undergo any trial till the 12th day (D12) to prevent practice effect. On the 12th day, each mouse was exposed to another probe trial for duration of 90 seconds to assess the long-term retention memory. The latency, (LT; time taken to reach the target hole for the first time) and the Time Spent in Target Quadrant (TSTQ; the quadrant that contained the target hole) were recorded for each treatment group.

Treatment protocol

A total of 20 mice employed in the study were shared into four different groups; each group comprising of five animals. No treatment was given to all the mice in the pre-training and probe phase. However, the mice received treatment in each day of the acquisition phase. All the mice were tried on the maze 45 minutes after their respective treatments on each day of the acquisition phase. The treatment protocol is as follows:

Group I (control group): Animals were treated with normal saline 10 ml/kg, i.p.
Group II: Animals were treated with piracetam 200 mg/kg, i.p.
Group III: Animals were treated with captopril 10 mg/kg, i.p.
Group IV: Animals were treated with donepezil 0.5 mg/kg, i.p.

Statistical analyses

Performance indices (LT and TSTQ) recorded on D5, were compared between treatment groups using one-way ANOVA. Similarly, performance indices recorded on D12 were compared between treatment groups using one-way ANOVA. A probability level of $p<.05$ was considered statistically significant. Calculations were performed using GraphPad Prism, version 8.0.2.

RESULTS

The results in Figure 1a indicate that there is a significant difference in latency among treatment groups $F(3,19)=108.93$, $p=.001$. Further statistical analysis reveal

that the mice treated with piracetam, captopril and donepezil had significantly lower latency scores than the mice in the control group (p=.001). This finding supports the fact that all the test drugs (piracetam, captopril and donepezil) produced significant improvement in short-term memory. Moreover, the results also reveal that the donepezil-treated mice produced a significantly lower latency scores compared to captopril (p=.001) but did not produce any significant difference when compared with the piracetam-treated mice (p=.329). In other words, mice treated with donepezil exhibited higher short-term memory activity than the captopril group, but no difference in short-term memory effect was recorded between the donepezil and piracetam group.

Evaluation of short-term memory

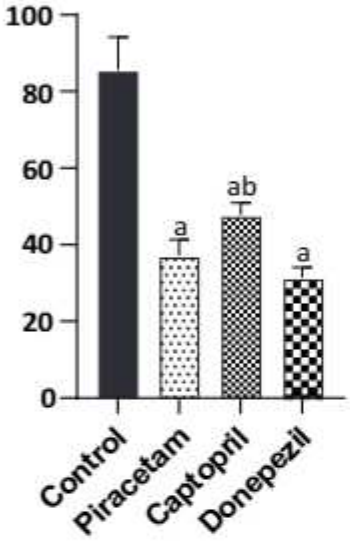

Fig. 1(a) Latency (D5)

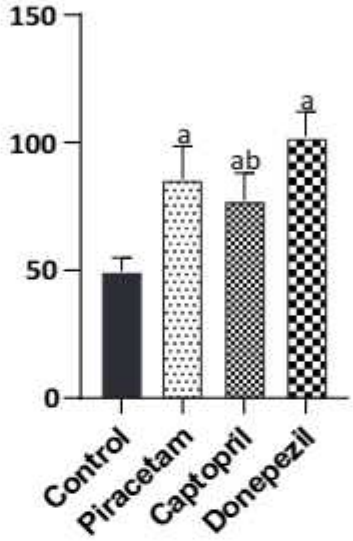

Fig. 1(b) TSTQ (D5)

ap<.05 considered when compared to control group; bp<.05 considered when compared to donepezil group.

Similarly, the result in Figure 1b show that TSTQ significantly varied among the treatment groups, F(3,19)=24.61, p=.001). Post hoc analysis reveal that all the mice treated with nootropic agents (piracetam, captopril and donepezil) demonstrated longer TSTQ compared with the mice in the control group (p<.01). This suggests that all test drugs produced an improvement in short-term memory. The results also indicate that the donepezil-treated mice had a significantly longer TSTQ than the captopril-treated mice (p=.005), but no significant difference existed between donepezil and piracetam (p=.076). In other words, mice in the donepezil group demonstrated improvement in short-term memory activity when compared with the captopril group, and no significant difference was found between donepezil and piracetam.

Evaluation of long-term memory activity

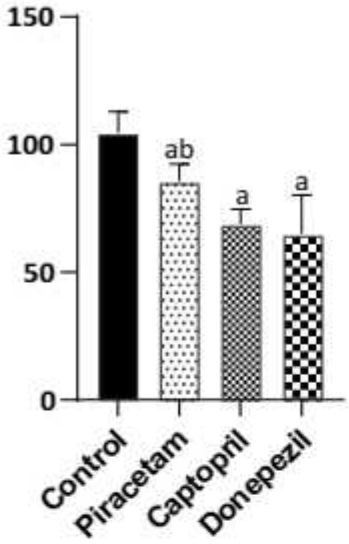

Fig. 2(a) Latency (D12)

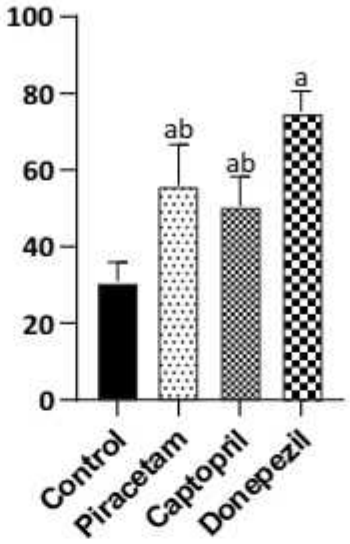

Fig. 2(b) TSTQ (D12)

ap<.05 considered when compared to control group; bp<.05 considered when compared to donepezil group.

The results of analysis in Figure 2a reveal that a significant difference exists in latency scores for all the treatment groups, $F(3,19)=17.32$, $p=.001$). Post hoc comparison analysis further indicate that latency scores of mice treated with test drugs were significantly lower than the mice in the control group ($p<.01$). This implies that all test drugs, including donepezil, piracetam and captopril produced improvement in long-term memory. The results also show that the donepezil-treated mice had a significantly lower latency than the mice in the piracetam-treated group ($p=.019$), but the difference in latency between the donepezil and the captopril-treated mice was insignificant ($p=.925$). Furthermore, the results indicate that the mice in the donepezil group exhibited higher long-term memory effect than piracetam, but had no difference in effect when compared with captopril.

Similarly, the results in Figure 2b reveal a significant difference in TSTQ among treatment groups, $F(3,19)=28.99$, $p=.001$. The results of post hoc comparison reveal that the mice treated with piracetam, captopril and donepezil had significantly higher TSTQ than the mice in the control group ($p<.01$). In addition, the results also reveal that the donepezil-treated mice demonstrated a significant difference in TSTQ when compared to the mice in piracetam ($p=.005$) and captopril ($p=.001$) groups. This result suggests that the mice in the donepezil group had a significantly longer TSTQ compared to other treatment groups.

DISCUSSION

The study examined the effect of some selected nootropics on short term memory (STM) and long term memory (LTM) with the aim of comparing their effectiveness. The finding of the present study reveal some important significant outcomes. First, the result of short-term memory testing reveals that, donepezil produced significant memory retention than captopril, but no significant difference in performance was recorded between donepezil and piracetam. This is evidenced by the decreased latency score recorded in the mice treated with donepezil as compared to captopril. The result on evaluation of long-term memory further reveals that donepezil exhibited a significant improvement in long-term memory than piracetam and had no significant difference in effect when compared to captopril. Donepezil was also able to produce better memory enhancing effect than both piracetam and captopril as revealed by the significantly longer time the mice spent in the target quadrant compared to both the piracetam and the captopril-treated groups. The results of our experiment therefore suggests that donepezil produced the highest memory-enhancing properties compared to piracetam and captopril in both short term and long term memory tests.

Consistent with the results of this study are observations from the work of Narimatsu and colleagues who reported that donepezil significantly improved spatial learning function in mice.[55] Although no clear explanation can be presented for the distinct nootropic activity of donepezil over piracetam and captopril, nevertheless, we may attribute this effect to the lipid soluble property of donepezil and its ability to cross the blood-brain-barrier.56 Donepezil is a highly active CNS-penetrating cholinesterase inhibitor that can inhibit acetylcholinesterase and butyrylcholinesterase enzymes in both central and peripheral nervous systems, thereby improving cognition.[57]

Similar argument may also be raised for captopril because the drug also crosses the blood-brain-barrier.[58] However, due to the numerous substrates for the angiotensin-converting enzyme, the neurochemical explanations responsible for their nootropic activities remain cloudy.[42] Several clinical studies have suggested that captopril is able to improve learning and memory through their centrally mediating properties.[59-62] A recent study by Nade and colleagues[63] suggested that the cognitive enhancing effects of Angiotensin Converting Enzyme Inhibitors (ACEi) may be due to inhibition of Cholinestrase (ChE) enzymes in the brain or by regulation of antioxidant system or increase in the formation of angiotensin IV. Conversely, another study has suggested that ACEi may play a major role in the pathogenesis of Alzheimer's disease because they block the conversion of more neurotoxic Aβ 1-42 into nontoxic Aβ1-40 by ACE and promote Aβ1-42 deposition in the brain of mice.[64]

On the other hand, piracetam, which also produced a lesser nootropic effect as compared to donepezil is a water-soluble racetam. This property gives piracetam poor blood-brain-barrier permeability and renders it less potent unlike other racetams such as aniracetam, which are lipophilic and can readily cross this barrier.[65] Piracetam is thought to trigger an increase in glucose and oxygen consumption in the brain and consequently promotes cognitive improvement. For example, past studies have found brain oxygen consumption[66] and interactions with glucose oxidation[67] to be increased mostly during periods of insufficient neuronal oxidation following piracetam ingestion. Even though the centrally mediating activities of piracetam have been reported, the exact mechanisms underlying the enhancement of glucose and oxygen consumption in the brain are currently not established.[68]

Pharmacokinetic evaluation of donepezil has shown that it has a half-life of 70-80 hours (69) and is slowly eliminated from the body.[70] In comparison, piracetam and captopril have shorter half-lives of about 5-6 hours[71] and 2 hours[72] respectively. The relatively longer half-life of donepezil may have influenced the better long-term retention recorded with donepezil on D12 as compared to piracetam and captopril. It is however imperative to note that the elimination half-life does not necessarily reflect the time to recovery from drug effects. Elimination half-life is an estimate of the time needed to reduce the drug concentration in the plasma by half.[73] For instance, lipid-soluble drugs such as donepezil may still be active in the CNS, even if they are only half-detectable in the blood at 70 hours.

CONCLUSION

Our study establishes the significant effects of nootropic drugs on the stimulation and facilitation of learning and memory in mice. We also found out that among the test drugs, donepezil demonstrated the highest nootropic activity. There is a clear implication of these results for the design of future studies. It is proposed that donepezil should be considered as a standard (positive) test drug when reliable data with regards to testing of agents for cognitive enhancing properties are to be generated. Besides being used as a first line palliative treatment of AD, donepezil should also be considered as a drug of choice in healthy individuals who seek to enhance their memory in order to gain competitive advantages. However, it would be worthwhile to explore the underlying mechanism of action for the observed nootropic effect that distinguishes donepezil as a better cognitive enhancer.

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