Effects of Beta-blockers on Memory in Veterans at the Ann Arbor Veterans Affairs Hospital

by

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Abstract

The purpose of this study was to examine the effects of beta-blockers on memory in patients at the Ann Arbor Veterans Affairs Hospital. Tests scores from a standard neuropsychological screening battery at the Ann Arbor Veterans Affairs Hospital, were compared between patients taking beta-blockers versus patients not taking beta-blockers, controlling for age and level of education. There was no statistical significance between the two groups. Results suggest that in non-demented, non-delirious older adult inpatients in an extended rehabilitation setting, regularly prescribed doses of beta-blockers do not adversely affect memory. More detailed analysis including measurable doses of beta-blockers should be conducted in the future.

Effects of Beta-blockers on Memory in Veterans at the Ann Arbor Veterans Affairs Hospital

Time trends have shown that the use of beta-blockers in older adults have been increasing annually (Smith, Chan, Jeannie, Rea, Wiggins, Gottdiener, Lumley, & Pasty, 2004). On November 14, 2005, the *New York Times* reported that beta-blockers (especially atenolol) were the fourth most-prescribed drug in the United States, with 44 million prescriptions yearly (Berenson, 2005). Apart from its ability to reduce mortality, the quality of life of patients on beta-blockers should also be addressed. Standard indicators of the quality of life include wealth and employment, built environment, physical and mental health, education, recreation and leisure time, and social belonging (Johnston, Gregory, Watts, Whatmore, & Pratt, 2009). In this study, we were interested in the impact of beta-blockers and memory- an important part of mental health.

Previous research on beta-blockers on cognition has yielded contradictory conclusions - many conclude that beta-blockers have no effects on cognition (Deary, Capewell, Hajducka, & Muir, 1991; Dimsdale, Newton, & Joist, 1989; Powell, Pickering, Wyke, & Goggin, 1993; Pérez-Stable, Halliday, Gardiner, Baron, Hauck, Acree M. & Coates, 2000), some conclude that beta-blockers have negative effects on cognition (Hartley, Ungapen, Davie, & Spencer, 1983; Lichter, Richardson, & Wyke, 1986; Richardson, & Wyke, 1988; Solomon, Hotchkiss, Saravay, Bayer, Ramsey, & Blum,1983), and some studies have even found positive effects on memory (Dimsdale, Newton, & Joist, 1991; Quervain, 2007). Hence, there is a need to reexamine the effects of beta-blockers on memory. The present paper describes a study of beta-blockers specifically on memory.

Although there is a large literature, this literature is inconsistent for two reasons. Firstly, almost half of these articles are based on small sample sizes, i.e less than 20 subjects. Secondly, previous tests have been too broad – testing all aspects of brain functioning. Neuropsychiatric testing measures a wide array of mental abilities and beta-blockers do not seem to affect all the different aspects of brain functioning; memory, however, appears to be specifically affected (Dimsdale et al., 1989). This study tries to overcome the unreliability by using a sample size of 469 patients and focusing on memory aspects of neuropsychological tests.

Biochemistry of Beta-blockers

Beta-blockers, also known as beta-adrenergic blocking agents, are medications that reduce blood pressure. Examples of beta-blockers include Acebutolol (Sectral), Atenolol (Tenormin), Bisoprolol (Zebeta), Carvedilol (Coreg), Metoprolol (Lopressor, Toprol XL), Nadolol (Corgard), Nebivolol (Bystolic) and Propranolol (Inderal LA) (Mayo clinic staff, 2008).

Beta-blockers differ by cardioselectivity, lipid solubility, and the presence or absence of intrinsic (agonist) sympathomimetric activity (ISA). As lipid solubility increases, the liver metabolizes more of the drug, more of the drug enters the brain, and its duration of action is shorter. As lipid solubility decreases, the drug is eliminated by renal excretion, less of the drug enters the brain, and its duration of action is longer. The most lipid-soluble drugs (lipophilic) - propranolol, penbutolol, and carvedilol are preferred in the presence of renal disease. Intermediate lipid-soluble drugs are metoprolol, prondolol and timolol. The least lipid-soluble drugs (lipophobic) atenolol,

betaxolol, carteolol, celiprolol, esmolol, sotalol and nadolol are preferred in the presence of liver disease (Habermann, 2008).

Atenolol a beta-1 (ß-1) cardioselective adrenoreceptor blocking substance, actively restricts certain hormones and neurotransmitters, thereby controlling the rate and force of contraction, consequently reducing blood pressure. The human body contains receptors that act to receive chemicals released from glands or nerves. The adrenal gland releases adrenaline (epinephrine) and in the sympathetic *flight or fight* response, the nerves secretes noradrenaline (norepinephrine). The hormone (adrenaline) facilitates the conversion of ATP to cAMP. The complimentary receptors for these chemicals are alpha and beta-adrenergic. Sympathetic activity is communicated to tissues through involuntary (autonomic) nerve impulses and through the blood.

The endocrine system responds to beta-adrenergic receptor stimulation by increasing blood sugar levels, inducing a faster heart rate and producing stronger heart contractions all by means of secreting adrenaline. This results in an increase of blood pressure. Atenolol blocks the receptor targets on heart muscle cells and prevents epinephrine and norepinephrine from stimulating the cardiovascular system. The heart beats more slowly and with less force, thereby reducing blood pressure and minimizing cardiovascular stress. The beta-blockers induce a nitrate pathway, which give rise to vasodilatation (dilation of arteriolar resistance vessels), thus helping to reduce symptoms of arrhythmias and minimize cardiovascular stress (Encarta, 2003).

Although beta-blockers have been associated with cognitive effects, hypertension itself may also have cognitive effects. Hypertension increases the risk of cerebro-vascular diseases such as stroke and may also have a role in the development of vascular cognitive

impairment and vascular dementia (Rigaud, Hanon, Bouchacourt, & Forette, 2000; Prince, 1997). Kaplan, (2001) has shown that the brain benefits from lowering abnormally elevated blood pressure and that reduction of hypertension protects the brain from stroke and cognitive impairment in later life. Neuropathological and neuropsychological investigations have shown that hypertensive patients more often have areas of white matter hyperintensity and ventricular enlargement compared to normotensive individuals (Harrington, Saxby, McKeith, Wesnes, Ford, 2000).

It is documented that there is an association between hypertension and reduced cerebral blood flow and vascular dementia. Longitudinal studies have also suggested that hypertension in midlife is associated with cognitive impairment later in life (Amenta, Mignini, Rabbia, Tomassoni, &Veglio, 2002). There is some understanding of the biological pathways of beta-blockers on hypertension. Although the exact biological pathways of the effect of beta-blockers on cognition have not been found, it is clear that there is an association between beta-blockers and cognition.

Previous findings on the role of beta-blockers in cognition

Previous research on beta-blockers of cognition has yielded conflicting conclusions. Hence, there is a need to critically access and review some of these studies.

No effects on cognition

Dimsdale et al. (1989) conducted a review of fifty-five studies of cognitive side effects of beta-blockers. They found that across all beta-blockers and all cognitive domains, the drugs led to improved functioning in 16% of observations and worsened functioning in 17%, with no significant effect in the rest. They also established from previous studies that memory, learning, and abstraction (quality of dealing with ideas

rather than events) was studied less frequently. The perceptual motor cognitive domain was the most widely studied and was frequently affected by beta-blockers. However, there was no consistent evidence of a trend for lipophilic beta-blockers, which as discussed earlier entered the brain and should affect cognition, to affect cognition more than lipophobic beta-blockers (less lipid-soluble drugs). The drugs also seem to increase sedation; however, in these studies there was no evidence for a differential effect across lipophilic vs lipophobic beta-blockers.

Likewise, Deary et al. (1991) conducted a double blind, double-dummy, randomized cross-over trial which compared the effects of atenolol (50 or 100 mg once daily) and captopril (25 or 50 mg twice daily), each taken for 6 weeks and their effects on memory, information processing ability, mood states and trait anxiety. Eighteen patients with mild to moderately severe hypertension were included. Patients undertook practice on the psychological test battery prior to the treatment phases of the study in order to minimize practice effects. There were no significant differences between the treatments, on any of the measures of memory or information processing. Patients reported feeling less anxious during treatment with atenolol. There were no differences between the drugs in their cognitive effects. However, reduction of anxiety by atenolol may mask possible effects of beta-blockers. A study needs to be done to compare patients on atenolol and no atenolol (control) which similar levels of anxiety and their effects on memory.

Similarly, in an investigation of the differential effects of three different anti-hypertensive medications (cilazapril, atenolol, nifedipine) on cognitive function, Powell et al. (1993) did not find a significant effect from any of them. A sub-group of patients participating in a large clinical trial of these three drugs, was randomly allocated between

the three drug conditions and received cognitive assessment at two points before the commencement of treatment and then after 12 and 24 weeks of treatment. Seventy-six patients began treatment, and 55 completed the full course. Tests of learning and memory (explicit and incidental) were specially designed for the study, with a different but comparable version administered on each assessment occasion (to reduce practice effects), in a fixed order. No significant differences between drug groups were found in any index of learning or memory, at any testing occasion.

The most recent study, a placebo-controlled trial among 313 men and women, 22 to 59 years of age, who had untreated diastolic hypertension (90 to 104mmHg) found that treatment of hypertension with propranolol had limited adverse effects on tests of cognitive function that were of questionable clinical relevance. Thirteen tests of cognitive function (7 tests measured memory or learning verbal information) were assessed at baseline, 3 months and 12 months. At baseline, there were differences between the groups in two tests of cognitive function – the continuous performance task error of commission and the Tuesday list from the California Verbal Learning Tests. However, neither of these differences were large. There were no statistically significant or clinically important differences in any of the other 12 tests of cognitive function (Pérez-Stable et al., 2000).

Negative effect of beta-blockers

Propranolol 40 mg was compared with a matched placebo tablet in its effect on the performance of anxious and non-anxious human volunteers in a study by Hartley et al., (1983). Subjects were prompted, by being given the first letter, to recall both difficult and easy words, drawn from selected verbal categories; propranolol impaired recall of

difficult items in the memory of anxious subjects, compared to placebo. There was also a three-way interaction between drug, anxiety and dominance. Results were interpreted as showing a central as well as peripheral role for propranolol in blocking adrenergic receptors' activity in anxiety.

Similarly, Solomon et al. (1983) found that verbal memory impairment was present in hypertensive and non-hypertensive patients taking methyldopa or propranolol hydrochloride, while hypertensive patients receiving only a diuretic did not show this deficit. Visual memory impairment was not seen in any of the groups tested. The majority of the subjects were unaware of their memory deficit, even when test results clearly revealed impairment. An earlier pilot study of 12 hypertensive patients receiving methyldopa or propranolol used a broad range of cognitive tests and also demonstrated impairment in verbal memory only, while other cognitive measures remained relatively unaffected.

Impaired memory associated with beta-blockers was also found in another experiment that compared the effects of different anti-hypertensive drugs. Memory function was assessed in a group of patients treated with either a beta-blocker (atenolol) or an angiotensin-converting enzyme inhibitor (enalapril) in a randomized, observer-blind study in moderate essential hypertension. The patients were assessed, on placebo and after 16 weeks of treatment on active therapy, by use of a series of 4 memory function tests related to everyday life. In the hypertension study group, 13 received atenolol and 12 received enalapril. In the atenolol group memory performance scores were consistently lower than in the placebo phase in 9 of 28 estimates of memory function. In the enalapril group there were no significant changes. The study indicated that atenolol

might produce mild memory impairment, whereas enalapril had no measurable effect on memory function (Richardson et al., 1988).

Lichter et al. (1986) conducted a randomized single-blind study to compare the performance on memory tests requiring recall of information relevant to everyday life of two groups of hypertensive patients. In the hypertension study group, 13 received atenolol and 12 received enalapril. In the atenolol group memory performance scores were consistently lower than in the placebo phase in 9 of 28 estimates of memory function: trials 1 & 6 (shopping list test), trial 4 (Logos), trials 2-7 (Telephone Extension numbers). In the enalapril group there were no significant changes. The study indicated that atenolol might produce mild memory impairment, whereas enalapril had no measurable effect on memory function.

Improvement in memory

In contrast, Dimsdale et al. (1991) found a significant improvement in memory. He conducted a double-blind study on the effects of non-lipophilic beta-blocker (atenolol) and lipophilic beta-blocker (metoprolol) on neuropsychological functioning, mood, sedation and sleep. Thirty-five hypertensive patients had their dosage of antihypertensive medication slowly reduced and a under went a 3-wk placebo washout. They were the randomized to receive double-bind either atenolol or metoprolol for 4 weeks. Neuropsychological testing was carried out twice, at the end of placebo period and after 4 wk of active treatment. Drug treatment with either drug was associated with a small but significant improvement in functioning on the Trails B, Digit Symbol substitution, Wechsler delayed memory and PSAT tasks.

Also in a double blind, placebo-controlled study, 42 healthy volunteers were

presented a set of words with variable emotionality and asked to learn them for recall. A day later, cortisone (25 mg), propranolol (40 mg), or both drugs were administered 1 hour before the test. Cortisone selectively impaired the recall of emotionally arousing words by 42%. Propranolol alone did not affect recall of either emotional or neutral words. A pharmacological blockade of B-adrenceptors prevents glucocorticoid-induced memory retrieval deficits in human subjects (Quervain, 2007).

Most of these studies have a sample size of less than a hundred with 313 being the largest. In each study, there were too many tests administered and hence too broad – testing all aspects of brain functioning, leaving them vulnerable to produced spurious results. The present study focuses only on measures of memory – using the Mini-mental state examination (MMSE), Rey Fifteen-Item Test of Memory and Hopkins verbal learning test (HVLT). Hence we aimed to overcome the unreliability of small sample size by using a sample size of 469 patients and limiting cognitive measures to memory aspects of neuropsychological tests.

Methods

All patients admitted to the Ann Arbor Veterans Affairs Hospital (AAVAH) Community Living Center (CLC) undergo a standard battery of cognitive tests. This is to provide quantification of cognitive functioning, and is helpful in treatment planning, identifying deficits and suggesting methods of compensation, and tracking changes in function over time.

A search was conducted on a database containing demographics, medical history, prescription and cognitive test data of patients who were evaluated in the CLC from January 2000 to 2009. The database was a compilation of self-collected data and a

preexisting database of 639 patients who were evaluated in the CLC from January 2000 to January 2007. Together, the data compiled from January 2000 to August 2009 consisted of 781 cases, before initial selection.

Participants

Participants were selected based on scores on certain subtests from the cognitive screen. Participants were excluded based on the following criteria: failing scores of measures of effort (Rey Fifteen Item Test of Memory [FIT] <9), failing scores on a brief mental screen (MMSE <18), and probable delirium (Memorial Delirium Assessment Scale [MDAS] >7). In the battery of measures used in the CLC, the HVLT-R (Hopkins Verbal Learning Test – Revised) is an effective of test memory, initial learning, learning with repetition, learning strategy, recall and recognition. Hence, this was our primary test of memory in this study.

After excluding patients who do not meet the mentioned requirements, 469 participants were included in the study. Of 469 participants, 447 were male (95.3%) and 22 were female (4.7%). Ages of participants ranged from 22 to 100, ($M=62.75$, SD = 11.51). Two hundred and thirty three were in the control group (Mean age = 60.61) and two hundred and thirty six people were in the medicated group (Mean age = 64.87). There was a significant difference in age (p <0.0001) and education (p=0.017) between the two groups, with the control group being older and less educated (Table 1).

Cognitive measures

The battery of measures in the community living center includes the mental state examination (MMSE), Wide range achievement test (WRAT4), Digit span, Rey Fifteen-Item Test of Memory, judgment, memorial delirium scale (MDS), trails A and B, Frontal

assessment battery (FAB), Hopkins verbal learning test (HVLT), Controlled oral word association test (COWAT), Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Brief Visuospatial Memory Test-Revised (BVMT-R) – of which we used Mini-mental state examination (MMSE), Rey Fifteen-Item Test of Memory, Hopkins verbal learning test (HVLT) and memorial delirium scale (MDS).

Mini Mental State Examination. It is widely used and a convenient test of cognition (Folstein & McHugh, 1975), because with limited resources and time, it gives a rough estimate of cognitive ability. Abilities measured include orientation, language (repetition, comprehension, reading, writing and naming), concentration (serial subtractions, backward spelling and following a three stage command), memory (three word registration, three word recall (MMSE-RT)) and visual processing and construction (copying a simple geometric figure). The total score is used as a screening measure of general mental status. The MMSE has proven to have good reliability and validity (Folstein et al., 1975).

An impaired score (total score less than 24) is usually used as an indicator of cognitive impairment (Tombaugh, McIntyre, & Nancy, 1992). In our study, we excluded participants with a score of 17 and below. Individuals with possible impairment (score between 18 and 23) were included because excluding them could also exclude those patients most affected by beta-blockers. Total MMSE score was used for participant selection. It was also used to compare the two groups for a measure of general cognitive ability and not memory itself. MMSE-RT was used as a measure of memory.

Memorial Delirium Assessment Scale. The MDAS (Breitbart, Rosenfeld, Roth, Smith, Cohen, & Passik, 1997) is a post screening measure of delirium. The interviewer

rates the patient on a scale from 0: none to 3:s evere for each category. Questions include assessments of impairment in consciousness, disorientation, perceptions, delusions, psychomotor activity, and sleep-wake cycles. It has been shown to be reliable and valid (Breitbart et al., 1997; Lezak, 1995). The patients who received a failing score (>7) on this measure were excluded because scores more than a 7 are highly indicative of delirium.

Rey Fifteen-Item Test of Memory. The FIT (Rey, 1964) is designed to assess effort and exaggeration or feigning of memory complaints (Boone, Salazar, Lu, Warner-Chacon, & Razani, 2002). Patients are given 10 seconds to study a sheet of paper with 15 items on it. Unknown to the patients, the items are related and can be easily categorized for easier memorization. The items include shapes, counting numerals and roman numerals. After ten seconds is over, subjects are asked to redraw the items that they saw on the paper. The overall task is very simple and even individuals who have sustained severe brain damage are able to pass the test. Research shows that if a patient scores 9 or below, the may be considered as putting forth poor effort (Goldberg & Miller, 1986; Reznek, 2005). Patients who scored less than 9 on this measure were excluded as this usually means that the results of the battery are not a true reflection of their mental abilities. Scores for this measure were also used only for participant selection and not for comparisons between groups. The FIT has proven to have high validity and reliability as a measure of effort (Goldberg & Miller, 1986; Taylor, Kruetzer & West, 2003).

Hopkins Verbal Learning Test. Tests such as the HVLT (Hopkins Verbal Learning Test – Revised) are effective in testing memory, initial learning, learning with repetition, learning strategy, recall and recognition (Brandt, 1991). A word list with

twelve words is read to the patient and the patient is asked to recall as many words as he or she can remember from the list, in any order. This process is repeated three times. The twelve words on the wordlist are related and can be categorized into three groups. However, the patient is not told that the words are related prior to testing.

After a 20-minute delay, a delay trial (HVLT4) is conducted - the patient is asked to recall as many of the words as he or she can from the list. Then, a yes/no format recognition test is administered, during which the original lists of words are presented amongst semantically related and semantically unrelated distracter words. HVLT trails 1 to 3 measures immediate memory and HVLT trail 4 and HVLT recognition trail measures delayed memory. All in all, the HVLT has shown to have good reliability and validity (Benedict et al., 1998).

Statistical Analysis

Bivariate correlations were computed to determine if there was potential correlation between demographic variables and outcomes. Data was analyzed using multiple linear regressions to determine the effects of beta-blockers on each of the following outcomes. MMSE total score (19-30), MMSE Three-word Recall (0-3), HVLT trials 1-3 (0-36), HVLT trial 4 (0-12). All analysis controlled for age, gender, and years of education. Beta-blockers was entered as a dichotomous variable. We predicted that patients who received beta-blocker medication would have significantly lower outcomes (test scores) then patients who did not receive beta-blockers.

Results

Preliminary analysis

The mean MMSE score for patients on beta-blockers was 26.95 (*SD*= 2.25) and for patients not on beta-blockers was 26.99 (*SD* =2.38). The mean HVLT trails 1 to 3 score for patients on beta-blockers was 17.57 (*SD* = 5.38) and for patients not on beta-blockers was 18.27 (*SD*=5.14). Please refer to Table 2 for details. Significant correlation was found between age and test scores, education and test scores. See table 3 for more details.

We found no interaction between age and beta-blocker (p=0.5844), and education and beta-blocker (p=0.1207), when predicting MMSE total scores. We also found no interaction between age and beta-blocker (p=0.7447), and education and beta-blocker (p=0.5864), when predicting HVLT Trail 1 to 3 scores. Hence we did not include the interaction term in our multi linear regression models.

Results from multi linear regression

There was no statistically significant difference in test scores for patients who were on beta-blockers versus patients who do not take beta-blockers, controlling for age and education level. There were some small differences in test scores between patients who take beta-blockers versus patients who do not take beta-blockers. Patients who took beta-blockers had 0.209 higher HVLT trail 1 to 3 scores (p=0.650), 0.140 higher HVLT trail 4 scores (p=0.624) and 0.145 higher HVLT recognition scores (p=0.522) compared to patients who did not take beta-blockers. The groups also did not differ on MMSE scores. However none of these differences were statistically significant.

Discussion

There was no statistical significance between the individuals taking beta-blockers and individuals not taking beta-blockers on measures of general mental status and memory. These results differ from previous findings of negative effects (Hartley et al., 1983; Lichter et al., 1986; Richardson et al., 1988; Solomon et al., 1983) and positive effects (Dimsdale et al., 1991; Quervain, 2007) of beta-blockers. Our results suggest that in non-demented, non-delirious older adult inpatients in an extended rehabilitation setting, regularly prescribed doses of beta-blockers do not adversely affect memory. There are many possible reasons as to why our results are different from previous findings.

Firstly, it may be possible that the patients have developed tolerance to beta-blockers over their course of medication. There have yet to be any data published that purposefully studied if patients developed tolerance and its effects on memory. However, studies have shown that there was little changes in blood pressure and heart rate as beta-blocker dosages increased from 100% to 125% and 150% of the original dosage (Krum, Ninio, MacDonald, 2000; Tandon, McAlister, Tsuyuki, Hervas-Malo, Dupuit, Ezekowitz, Cujec & Armstrong, 2004). This meant that patient's body and brain's response to beta-blockers may have diminished and this phenomenon meant that there would not be any significant effects on memory.

We were not able to ascertain how long the patients have been taking beta-blockers. Hence, we were not able to find out if they had developed tolerance and whether this tolerance affected their memory. Hence, a future study can be done to compare the memory of patients who have taken beta-blockers for a long time versus patients who

have just started taking beta-blockers.

It may also be possible that the majority of the patients in our study were taking lipophobic drugs. Lipophobic drugs have low lipid solubility and are eliminated by renal excretion. Hence, less of the drug enters the brain and has less detrimental effects on the brain. Although Dimsdale et al. (1989) found no consistent evidence of a trend for lipophilic drugs to affect cognition more than lipophobic drugs, more studies can be done to compare cognitive effects between patients on lipophilic drugs and lipophobic drugs, with emphasis on memory.

There may also be a difference between older and newer beta-blockers on memory. There exists a wide range of pharmacological routes to the treatment of essential hypertension. The older agents, including diuretics and B-adrenoceptor blockers, are very effective in reducing blood pressure but they also cause many adverse effects, such as unwanted metabolic changes (Ames, 1986; Kaplan, 1986; Knochil, 1984; Murphy et al., 1982). The metabolic changes are dose-dependent and are difficult to repeat after 1 year. Newer drugs including calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors, are no more effective than the older drugs but there is some evidence that they lack the adverse metabolic effects (Hedner et al., 1987; Pollare et al., 1989). It is possible that memory impairments described in other literature occur in patients taking only the older class of anti-hypertensive medication and our patients took newer classes of beta-blockers. Pharmaceutical companies may have made adjustments to the newer beta-blockers. Hence, they have no effect on cognition and specifically memory.

Beta-blockers as a class have many undesirable effects including drowsiness, lethargy, sleep disturbance, visual hallucinations, depression, blurring of vision and

dreams/nightmares that may affect their attention during cognitive tests. They also have pulmonary side effects such as increased airway resistance in asthmatics, and peripheral vascular side effects such as cold extremities, Raynaud's phenomenon, erectile, and orgasmic dysfunction **(**Messerli et al., 2002). Hence, in other studies, it might be drowsiness and lethargy that cause effects on memory and not beta-blockers per se.

However, in another study, 167 men treated with beta-blockers showed a proportionally lower prevalence of sleep complaints (Gislason, & Almqvist, 1987). Hence, patients on beta-blockers might not have been affected by sleep enough to affect their test scores. This supported our findings that there is no significant difference in test scores between patients on beta-blockers and patients not on beta-blockers. Given the design of our study, it is difficult to know whether memory functioning was confounded by lethargy or sleep disturbances.

There is even some data suggesting that untreated hypertension is itself associated with cognitive effects (Reitz et al., 2007). Hence, it might just be hypertension that is affecting tests score on memory rather than the effects of beta-blockers. A study to compare memory between hypertensive patients on beta-blockers versus hypertensive patients that are not treated has to be conducted.

We realize that by excluding individuals based on the MDAS for delirium we may have excluded some individuals showing cognitive impairment due to beta-blockers. This might be possible because there was a case report of acute delirium induced by metoprolol (Fisher et al., 2002) and one other report of metoprolol-induced delirium perpetuated by propaferone (Ahmad, 1991).

Drug interactions may have an effect on test results. Many of the older adult inpatients in the community living center (an extended rehabilitation setting) in the Veterans Affairs hospital have other medical problems and many are on several different types of medications, many of which cause fatigue and delirium, which might affect test performance and have an impact on the test scores.

There are important implications of this study. The results suggest that use of beta-blockers at a level commonly prescribed in a nursing home setting does not appear to have a significant impact on memory. This can help practitioners and health care providers to decide what type of anti-hypertensive medication are suitable for a patient. If possible, a similar study should be replicated. More detailed analysis including placebos and measurable doses of beta-blockers should also be conducted in the future.

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Table 1

Descriptive statistics of demographic variables

	Beta-blocker vs Not taking beta-blockers		
Beta-blocker	Age	Education	Gender
Yes	60.61 (11.71)	13.35 (4.38)	7/236 = 2.97% Female 229/236 = 97.03% Male
No	64.87 (10.92)	12.57 (2.19)	15/233 = 6.44% Female 218/233 = 93.56% Male

Table 2

Descriptive statistics of test scores

	Beta-blocker vs Not taking beta-blockers	
Test	Beta-blockers	Not on beta-blockers
MMSE total	26.95 (2.25)	26.99 (2.38)
MMSE Recall (Ball, Flag and Tree)	2.14 (1.13)	2.30 (0.85)
HVLT Trails 1 to 3	17.57 (5.38)	18.27 (5.14)
HVLT Trail 4	5.33 (2.98)	5.59 (3.25)
HVLT Recognition Trail	10.29 (2.75)	10.32 (1.94)

Mean (Standard deviation)

MMSE = Mini Mental Standard Examination

MMSE Recall = Mini Mental Standard Examination Recall Trials

HVLT Trails 1 to 3= Hopkins Verbal Learning Test Trails 1 to 3

HVLT Recognition Trail = Hopkins Verbal Learning Test Recognition Trail

Table 3

Correlation between demographic variables and outcome

Test	Age	Education	Beta-blocker (Yes/No)
MMSE total	-0.211*	0.149*	-0.005
MMSE Recall (Ball, Flag and Tree)	-0.182*	0.044	-0.075
HVLT Trails 1 to 3	0.375*	0.118*	-0.067
HVLT Trail 4	-0.240*	0.136*	-0.036
HVLT Recognition Trail	-0.335*	0.061*	-0.036

Note. * $p < 0.05$

Table 3

Parameter estimates for covariates in multiple linear regression model

Test	Intercept	Age	Education	Beta-blocker
MMSE total	28.34*	-0.045*	-0.005*	0.243
MMSE Recall (Ball, Flag and Tree)	3.08*	-0.015*	0.011	-0.081
HVLT Trails 1 to 3	26.38*	-0.173*	0.173*	0.209
HVLT Trail 4	7.93*	-0.065 *	0.119*	0.140
HVLT Recognition Trail	11.3*	-0.029 *	0.061	0.145

Note. * $p < 0.05$