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COMPARISON OF NORTRIPTYLINE AND BUPROPION IN MAJOR DEPRESSIVE DISORDER AMONG

ELDERLY PATIENTS

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# ABSTRACT

**Objective:** To compare the effectiveness of notriptyline and buproprion in treating major depressive disorders in elderly patients.

**Design:** Randomized double blind controlled study with 8 weeks follow up.

**Place and Duration of Study:** The out patient clinics at the Ghaem and Avicenna Hospital, Faculty of Medicine of the University of Mashad from March 2005 to September 2006.

**Subjects and Methods:** We selected 52 elderly outpatients who had non psychotic major depressive disorder according DSMIV criteria and they were allocated to two group who received nortryiptiline (at a dose of up to 150 mg per day) and bupropion (at a dose of up to 225mg per day). We used Hamilton Rating Scale for depression (HRSD; Hamilton, 1959), Mini Mental Status Exam (MMSE), and The Geriat- ric Depression Scale-30 (GDS-30) on the first visit.

**Results:** Both treatments were efficacious, and there were no statistically significant differences be- tween the two antidepressant classes with respect to efficacy (pvalue<0.05).

**Conclusions:** For elderly depressed patients who completed a 8 week treatment trial, both nortriptyline and bupropion exhibited good efficacy and few side effects. There was no difference between groups in the response rate or the severity of side effects due to drug treatment.

**Key words:** Major Depression, Elderly, Hamilton Rating Scale for Depression (HRSD), Mini Mental Status Exam (MMSE), Geriatric Depression Scale 30 (GDS-30).

# INTRODUCTION

Untreated patients with depressive disorders are at risk of social and psychological problems, as well as disability resulting from co morbid and secondary disorders. This co-morbidity is associated with a more severe presentation of depression, including greater risk of suicide.

Although the geriatric age group constitutes the most rapidly growing segment of the population1 de- pression is often unrecognized, under-diagnosed and inadequately treated in this group2, and the randomized clinical trials are limited to treatment of depressed eld- erly patients. It is not clear which class of drugs is supe- rior, in terms of efficacy or tolerability, in the treatment of depressed elderly patients. Data from young adult stud- ies and clinical experience suggest that pharmacologic

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treatments are safe and effective for depressed elderly patients3, but attention needs to be given to developing rational strategies for drug selection in order to mini- mize deleterious side effects, to which medically ill eld- erly patients may be vulnerable4-6. Some studies have shown that safety and tolerability of SSRI’s7, tricyclics8, reversible inhibitors of monoamine oxidase-A9 and atypi- cal antidepressants in late-life major depression are rela- tively same. However the use of psychotropic agents to treat depression in medically ill elderly patients requires consideration of special pharmacokinetic and pharma- codynamic factors in drug selection10 and some of the newer drugs may be more appropriate long-term op- tions for the treatment9,11. Because of the risk of anticho- linergic side-effects of tricyclics such as falls related to postural hypotension, cardiac toxicity12,13, and cognitive impairment the new generation drugs, represent the first therapeutic choice in most cases of depression14. How- ever, Most studies of efficacy of the newer antidepres- sants as compared to tricyclics in the treatment of late- life major depression have focused on Serotonin Spe- cific Reuptake Inhibitors15. Some evidence demonstrates that the Serotonin Specific Reuptake Inhibitors may also induce severe side effects, such as insomnia, waight change agitation and serotonin syndrome16. In addition,

they may be less efficacious in the treatment of severe depression, as compared to trisyclics. For elderly pa- tients with major depressive disorder, secondary amine tricyclic antidepressants, such as nortriptyline, are per- ceived to be more appropriate17. These are well toler- ated drugs among the tricyclics, they continue to be re- lied upon and are among the most widely prescribed of such medications.

Bupropion has an apparently different mechanism of action than TCAs and represents a possible treat- ment for the TCA non-responder18,19. Its main mecha- nism of action is believed to be via dopamine and nora- drenalin reuptake inhibition20.The results from both double-blind and open treatment with bupropion dem- onstrate that this drug offers a promising alternative therapy for patients with a history of poor response to TCAs21. The risk of a seizure in patients receiving equally therapeutic doses of tricyclic antidepressant drugs and bupropion was same22. But some cognitive changes might be normalized in depressive patients who use bupropion23.

Considering the importance of the treatment and management of depression in elderly patients, we un- dertook this single blind-trial to assess and compare the efficacy and safety of nortriptyline and bupropion on major depressive disorder in the old age population.

# SUBJECTS AND METHODS

This study was conducted from March 2005 to Sep- tember 2006 at the outpatient psychiatry clinic of Avicenna Hospital, a referral center for psychiatry in the north east of Iran. The study was performed in accor- dance with the current revision of the Declaration of Helsinki (Hong Kong, 1989) and was approved by the ethics committee of Mashhad University. Written in- formed consent was obtained from the patients, their family, or an authorized representative. Finally, 52 pa- tients who met the DSM-IV criteria for Major depressive disorder and satisfied the selection criteria presented below were randomly assigned to receive treatment: 28 nortriptyline and 24 bupropion.

Patients more than 60 years old were screened for major depressive disorder using semi-structured clinical interview. The patients and their families were interviewed by a psychiatrist. Demographic information, medical and psychiatric history was obtained. Each pa- tient underwent a medical and neurological examina- tion before randomization and at completion of the study. Laboratory tests obtained included a complete blood count, fasting blood sugar, liver function tests, electro- lytes, blood urea nitrogen, serum creatinine, thyroid func- tion test, and urine analysis. For the psychiatric evalua- tion, we used Hamilton Rating Scale for depression (HRSD; Hamilton, 1959), Mini Mental Status Exam (MMSE), and The Geriatric Depression Scale-30 (GDS- 30) on the first visit.

Inclusion criteria were any male or female with a DSM-IV diagnosis of major depressive disorder (Ameri-

can Psychiatric Association, 1994), age more than 60 and HRSDscore of 20 or more. Patients were excluded from the study if they had severe anxiety symptoms or grief reaction in the previous 6 months. Patients with any clinically important medical disease or abnormality on physical examination, such as recent head trauma or other brain injuries, thyroid abnormality , acute heart disease, as well as other Axis 1 psychiatric disorders, or cognitive disturbances (MMSE <25) were also ex- cluded. The patients were included if no pharmacologi- cal or non-pharmacological drugs with psychotropic ef- fects was used within 4 weeks before the study period. Based on selection criteria, 52 patients were recruited who met DSM-IV criteria on the structural clinical inter- view for Major depressive disorder.

Study medication was administered under single

-blind conditions as oral tablet of either nortriptyline and bupropion for 8 weeks. The patients were assigned ran- domly to receive one of the two drugs, with usual dos- age for elderly patients (nortriptyline, 150mg/day, bupropion 225 mg/day). The dose of study medication was increased gradually according to a fixed incremen- tal schedule. Nortriptyline dosage was increased 25 mg/ week. Bupropion was increased in75mg increments at a minimum of 2 weeks dependent upon tolerability and response. nortriptyline was dosed equally on a triple- daily administration regimen and Bupropion was used twice daily.

Clinical improvement was assessed by a psychia- trist and a psychologist blind to the treatment. Efficacy was evaluated using the HRDS at baseline and after 2, 4, and 8 weeks. HRSD was used as an outcome mea- sure for our study. Response to treatment was defined as a decrease of at least 50% in the HRDS total score from baseline.

Clinical assessments were carried out on each visit. Patients were questioned about any new symp- toms or common adverse events. Spontaneously re- ported adverse events were detected by clinical evalua- tions and patients’ reports. Safety was assessed by means of physical examination, and compliance was measured by patients and family reports on each visit. Withdrawal of the patients from the trial was planned in case of lack of efficacy (based on structured interview), or severe adverse events such as gastrointestinal up- set, headache, dizziness, and sedation.

All data was analyzed by SPSS 11.5, and p <

0.05 was considered to be statistically significant. The results are expressed as mean (standard deviation [SD]). *t*-test was used to compare the nortriptyline and bupropion groups on demographic features of age, age at onset, and HRSD score on each visit. To compare the level of education, gender, residential status and past history of major depressive disorders, chi square test was used. GDS and MMSE had non-symmetric distribu- tion and therefore were compared by Mann Whitney

test. Repeated-measurement test was used to compare the HRSD score of the baseline and the end of study period in each group.

# RESULTS

Subjects

A total of 52 patients who met the DSM-IV criteria for Major depressive disorder entered the study at Avecina Hospital in Mashhad. Twenty-eight patients were randomly assigned to treatment with nortriptyline and 24 to bupropion.

The mean demographic characteristics and baseline scores of depression of the two groups at baseline were similar (Table 1). Participants in the bupropion group had a slightly higher mean GDS total score at baseline than those in the bupropion group which proved not significantly different using Mann Whitney Test (12.28+/-4.23 versus 12.54+/- 1.23, p=0.08). The mean MMSE score at baseline was 26.65+/- 4.56 in nortriptyline group and 27.83+/-0.65 in bupropion that was not significantly different using Mann whitney Test (Z=-0.6, p=0.7). Baseline score for HRSD was 34.69+/-6.66 and 33.45+/- 4.87 respec- tively for nortriptyline and bupropion groups, which again was not significantly different using *t* Test (*t*=0.09, p=0.96).

Both nortriptyline and bupropion had an antide- pressant efficacy and a steady decrease in the total HRDS scores for both groups was observed at week 8 (14.21+/

-2.21 Vs 14.9 +/-5.23) (Fig.1).

Patients in both groups showed clinically signifi- cant improvement. The mean difference in HRDS score at the beginning of study and after 8 weeks (HRDS 0 – HRDS 8) was greater in nortriptyline group but that was not significantly different ( p=0.29).

# Safety and tolerability

No clinically significant serious adverse events or changes in laboratory test results were observed during the study period. Vital sign and bodyweight did not change in either group. However 2 cases from bupropion and 4 from nortriptyline withdrawed from study: 2 pa- tients could not tolerate the sedation, 2 patients due to unknown reason.

# DISCUSSION

The current study was undertaken to evaluate the efficacy of nortriptyline and bupropion in the treatment of elderly patients with major depressive disorder. We have chosen nortriptyline as the representative of the TCA group because it is more likely to be toler- ated by the elderly than the former drug. Both treat-

Table 1

Demographic and characteristic variables of the patients in each group

|  |  |  |
| --- | --- | --- |
| **Variables** | **Nortriptyline (n=28)** | **Boprupion (n=24)** |
| * Age(year/Mean±SD) | 64.3±12.2 | 64.6± 15.4 |
| * Gender(number of male | 16 | 14 |
| * Educational level(number |  |  |
| Illiterates | 6 | 8 |
| Primary and secondary | 22 | 14 |
| Higher | 0 | 2 |
| * Marital Status |  |  |
| Single | 0 | 0 |
| Married | 26 | 21 |
| Widow | 2 | 3 |
| * First Episode(number) | 10 | 8 |
| * Duration of current episode(weaks/ Mean±SD) | 2.8±1.6 | 3.1±1.4 |
| * Family history of depression (number) | 4 | 1 |
| * MMSE ( Mean±SD) | 26.65+/- 4.56 | 27.83+/-0.65 |
| * HRDS ( Mean±SD) | 34.69+/-6.66 | 33.45+/- 4.87 |
| * GDS-15 (Mean±SD) | 12.28+/-4.23 | 12.54+/- 1.23 |

SD=Standard deviation- HRDS= Hamilton Rating Scale for depression - MMSE=Mini Mental Status Exam – GDS-15=Geriatric Depression Scale\_15

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Baseline** | **2nd week** | **4th week** | **8th week** |  |
| **34.69** | **30.68** | **19.85** | **14.9** | **Nortriptyline** |
| **33.45** | **28.43** | **18.22** | **14.21** | **Bupropion** |

Fig. 1: Antidepressant effect of nortriptyline and bupropion based on the change of total Hamilton Rating Scale for Depression



ments were efficacious, and there were no statistically significant differences between the two antidepressant classes with respect to efficacy, as measured by a 50% decrease in the HRDS scores. There are some reports which show that Bupropion can induce parkinsonism24, dyskinesias25 or cardiovascular effects26,27.These issues make some doubt to use bupropion in elderly pupolation who are at risk of movement disorders. In present study we did not find sever side effects associated with either of drugs.

In another study bupropion was as effective as amitriptyline in reducing depressive symptoms over a 6- month period, as measured by Hamilton depression and anxiety scales and Clinical Global Impression scores. Unlike amitriptyline, bupropion did not increase uric acid or cholesterol levels, and was not associated with weight gain. Bupropion was better tolerated than amitriptyline, the most commonly prescribed antidepres- sant28.

Study limitations include the lack of a placebo con- trol condition and nonmasked treatment delivery, al- though assessors of the primary outcome (Hamilton de- pression scale) were masked to treatment. While a pla- cebo control design could have helped to determine

whether improvement was due to spontaneous improve- ment or to nonspecific aspects of treatment, such a con- trol is not required to discern whether these two treatments differed. Further, switching to a placebo after two consecutive failed treatment trials would have raised insurmountable human participant concerns and likely would have limited generalizability if many participants refused random assignment. A blinded pla- cebo control condition could also have led to less vigor- ous dosing, given the high prevalence of multiple gen- eral medical conditions in our participants. Another limi- tation of the present study was its small sample size.

Despite these limitations the study findings have some implications. This study is the first we are aware of to have compared a tricyclic antidepressant with bupropion in elderly population. Although there is a sub- stantial literature demonstrating that depression in eld- erly patients responds to bupropion the literature on the compression between two drugs was less clear. Another important finding of this study was that there were no significant side effects on both medications. This might have arisen because of small sample size. However it could also be due to tact that the dosage of drugs in- creased slightly.

# CONCLUSIONS

For elderly depressed patients who completed a 8 week treatment trial, both nortriptyline and bupropion exhibited good efficacy and few side effects. There was no difference between groups in the response rate or the severity of side effects due to drug treatment. The findings need to be considered in the context of small sample size.

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