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 Geriatric Depression Scale-30 (GDS-30) on the first visit.

Results: Both treatments were efficacious, and there were no statistically significant differences between 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 population[1] depression is often unrecognized, under-diagnosed and inadequately treated in this group[2], and the randomized clinical trials are limited to treatment of depressed elderly patients. It is not clear which class of drugs is superior, in terms of efficacy or tolerability, in the treatment of depressed elderly patients. Data from young adult studies and clinical experience suggest that pharmacologic treatments are safe and effective for depressed elderly patients[3], but attention needs to be given to developing rational strategies for drug selection in order to minimize deleterious side effects, to which medically ill elderly patients may be vulnerable[4-6]. Some studies have shown that safety and tolerability of SSRI's[7], tricyclics[8], reversible inhibitors of monoamine oxidase-A[9] and atypical antidepressants in late-life major depression are relatively same. However the use of psychotropic agents to treat depression in medically ill elderly patients requires consideration of special pharmacokinetic and pharmacodynamic factors in drug selection[10] and some of the newer drugs may be more appropriate long-term options for the treatment[9,11]. Because of the risk of anticholinergic side-effects of tricyclics such as falls related to postural hypotension, cardiac toxicity[12,13], and cognitive impairment the new generation drugs, represent the first therapeutic choice in most cases of depression[14]. However, Most studies of efficacy of the newer antidepressants as compared to tricyclics in the treatment of late-life major depression have focused on Serotonin Specific Reuptake Inhibitors[15]. Some evidence demonstrates that the Serotonin Specific Reuptake Inhibitors may also induce severe side effects, such as insomnia, waight change agitation and serotonin syndrome[16]. In addition,

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they may be less efficacious in the treatment of severe depression, as compared to trisyclics. For elderly patients with major depressive disorder, secondary amine tricyclic antidepressants, such as nortriptyline, are perceived to be more appropriate[17]. These are well tolerated drugs among the tricyclics, they continue to be relied 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 treatment for the TCA non-responder[18,19]. Its main mechanism of action is believed to be via dopamine and noradrenalin reuptake inhibition[20].The results from both double-blind and open treatment with bupropion demonstrate that this drug offers a promising alternative therapy for patients with a history of poor response to TCAs[21]. The risk of a seizure in patients receiving equally therapeutic doses of tricyclic antidepressant drugs and bupropion was same[22]. But some cognitive changes might be normalized in depressive patients who use bupropion[23].

Considering the importance of the treatment and management of depression in elderly patients, we undertook 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 September 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 accordance with the current revision of the Declaration of Helsinki (Hong Kong, 1989) and was approved by the ethics committee of Mashhad University. Written informed consent was obtained from the patients, their family, or an authorized representative. Finally, 52 patients 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 patient underwent a medical and neurological examination before randomization and at completion of the study. Laboratory tests obtained included a complete blood count, fasting blood sugar, liver function tests, electrolytes, blood urea nitrogen, serum creatinine, thyroid function test, and urine analysis. For the psychiatric evaluation, 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 (American 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 excluded. The patients were included if no pharmacological or non-pharmacological drugs with psychotropic effects 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 interview 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 randomly to receive one of the two drugs, with usual dosage for elderly patients (nortriptyline, 150mg/day, bupropion 225 mg/day). The dose of study medication was increased gradually according to a fixed incremental 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 psychiatrist 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 measure 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 symptoms or common adverse events. Spontaneously reported adverse events were detected by clinical evaluations 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 upset, 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 distribution 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 respectively 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 antidepressant 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 significant 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 patients could not tolerate the sedation, 2 patients due to unknown reason.

DISCUSSION

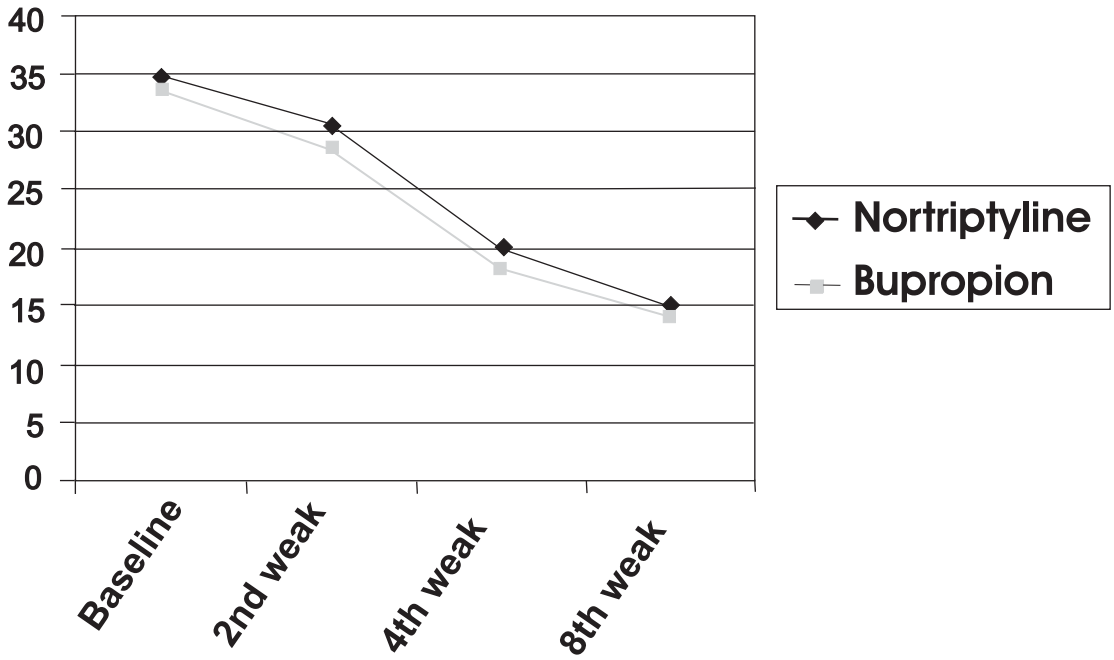
The current study was undertaken to evaluate the efficacy of nortriptyline and bupropion in the treatment of elderly patients with major depressive disorder. We have chosen nortriptyline as the representative of the TCA group because it is more likely to be tolerated by the elderly than the former drug. 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 Primary and secondary Higher	 6 22 0	 8 14 2
• Marital Status Single Married Widow	 0 26 2	 0 21 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 parkinsonism[24], dyskinesias[25] or cardiovascular effects[26,27].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 antidepressant[28].

Study limitations include the lack of a placebo control condition and nonmasked treatment delivery, although assessors of the primary outcome (Hamilton depression scale) were masked to treatment. While a placebo control design could have helped to determine whether improvement was due to spontaneous improvement or to nonspecific aspects of treatment, such a control 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 placebo control condition could also have led to less vigorous dosing, given the high prevalence of multiple general medical conditions in our participants. Another limitation 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 substantial literature demonstrating that depression in elderly 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 increased 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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