TREATMENT WITH HORMONE THERAPY AND CALCITRIOL DID NOT AFFECT DEPRESSION IN ELDERLY POSTMENOPAUSAL WOMEN: NO INTERACTION WITH ESTROGEN AND VITAMIN D RECEPTOR GENOTYPE POLYMORPHISMS

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Abstract

Objective—To examine the effect of hormone therapy and calcitriol on depression in elderly postmenopausal women and also to determine whether the response was associated with polymorphisms of estrogen receptor-alpha and vitamin D receptor.

Methods—In a double-blinded placebo controlled prospective trial involving 489 postmenopausal elderly women, a secondary analysis of depression was done. Geriatric Depression Scale was used to screen for depression. We used binary logistic regression to examine the effect of treatment on depression and one-way ANOVA to find relationship between gene polymorphisms and depression.

Results—There was no effect of hormone therapy (OR 1.65; 95% CI 0.66–4.12; $p = 0.277$), calcitriol (OR 1.15; 95% CI 0.43–3.11; $p = 0.772$) or hormone therapy with calcitriol (OR 1.01; 95% CI 0.36–2.80; $p = 0.979$) on depression. Neither polymorphisms of estrogen receptor-alpha (XbaI-beta=0.093, CI −0.337–1.350, $p = 0.239$ and PvuII-beta=−0.064, CI −1.171-0.491, $p = 0.421$) nor vitamin D receptor (BsmI-beta=0.044, CI −2.546–3.030, $p = 0.865$ and TaqI-beta= −0.015, CI −2.900-2.738, $p = 0.955$) were associated with depression.

Conclusion—In elderly post-menopausal women there was no effect of hormone therapy and calcitriol either individually or in combination with depression. Estrogen receptor-alpha and vitamin D receptor polymorphisms are not associated with depression or the response to intervention in elderly postmenopausal women. Additional trials are required to confirm these findings.

Keywords

hormone therapy; vitamin D; depression; estrogen receptor polymorphism; vitamin D receptor polymorphism and postmenopausal women

INTRODUCTION

Late-life Depression is common cause of disability in people over 65 years of age because of biological, psychological and social risk factors that come with age. The prevalence is

approximately between 8–39% and it varied in different settings[1,2]. This has become a public health burden because it leads to decreased quality of life and increased hospitalization[3] because it is often under diagnosed and undertreated[4] in primary care setting as many of them may not present with typical symptoms of depression such as sadness[5] or they may consider depressed mood as normal part of aging though it is not[6].

Older women were known to have higher risk of developing depression when compared to men[7]. This could be partly due to loss of estrogen with menopause because estrogen is known to have neuroprotective effects on brain[8] but when progestins are added to estrogens this effect may diminish[9]. Hormone therapy (HT) may improve the symptoms of depression in depressed people[10] or decrease the risk of developing depressive symptoms in older women[11], but this is unclear because in some studies HT does not stop the development of depressive symptoms in elderly postmenopausal women[12,13,14]. The exact role of estrogen still needs to be defined. The genomic actions of estrogen are exerted through two kinds of receptors-estrogen receptor-alpha (ER- α) and beta (ER- β). Two commonly known single nucleotide polymorphisms (SNP) of ER- α receptor are PvuII (rs2234693) and XbaI (rs9340799). Polymorphisms of the ER- α have been associated with psychiatric disorders like Alzheimer's disease[16] and one study has shown an association between ER- α genotype polymorphisms and depression in women[15] but their exact role in depression has not been clearly defined.

Elderly are also at higher risk of developing vitamin D deficiency due to decreased dietary intake, less sun exposure, restricted outdoor activity and a decreased capacity to produce enough calcitriol as a result of an age related decline in hydroxylation by kidneys. Besides playing a role in calcium homeostasis, vitamin D also has the potential for a neuroactive effect on brain function[17] through the vitamin D receptor (VDR). Low vitamin D levels may be associated with depression in elderly[18,19] and taking supplements may improve the symptoms of depression[20]. Despite these findings the associations are not conclusive because some studies did not find any association[21,22] and most of the studies that found an association between vitamin D and depression are cross sectional, observational or small sample studies with methodological problems. Although VDR genotype polymorphisms were shown to be associated with bone mineral density and risk of fractures[23], their role in the pathology of depression has not been clearly established.

There are few prospective studies that have evaluated the relationship between either HT and depression or vitamin D and depression. However to our knowledge there were no studies that evaluated the effect of HT given with vitamin D along with their individual effects on depression in elderly postmenopausal women. Also few studies examined the relation between ER-α gene polymorphisms and depression[24,25] and one study examined the association of VDR gene polymorphisms with depression[26]. In this 3- year double-blinded placebo controlled intervention study, the primary outcome was the effect of HT and calcitriol either individually or in combination on age-related bone loss in elderly postmenopausal women. However we also collected Geriatric Depression Scores (GDS) at baseline and at the end of 36 months (final visit) and the purpose of this paper is a secondary analysis of the longitudinal effect of hormone therapy and Vitamin D on depression along with the role of ER- α, VDR genotype polymorphisms and serum levels of estradiol, sex hormone binding globulin (SHBG) and testosterone.

METHODS

Participants in this study (STOP IT - Sites Testing Osteoporosis Prevention or Intervention Treatment) are 489 community dwelling elderly post-menopausal women aged between 65–77 years who were tested for the effect of HT and calcitriol either individually or in

combination on age-related bone loss. Participants were randomly assigned to one of the four groups by computer generated randomization list-conjugated equine estrogens 0.625 mg/daily (ET) in hysterectomized women (or combined with medroxyprogesterone acetate 2.5 mg/daily (EPT) in women with intact uterus); Calcitriol 0.25 g twice a day; combination group (HT plus calcitriol) and matching placebos. All the women were given two pills (placebo and intervention pill) and placebo pills were made to appear identical to the treatment pills. Compliers in this study were defined as those who were 80 percent or more compliant in taking the study medication. It was estimated by pill counts. Compliance at 36 months was 92% in the group taking conjugated estrogens, 94% in the group taking medroxyprogesterone acetate, 93% in the group taking calcitriol and 92% in placebos.

Women who had chronic illness, primary hyperparathyroidism or active renal stone disease, and who were taking certain medications, such as bisphosphonates, anticonvulsants, estrogen, fluoride, or thiazide diuretics in the last 6 months were excluded from the study. The protocol was reviewed and approved by IRB and all participants were randomized only after signing an informed consent form. NIH established a Data Safety and Monitoring Board to monitor the study. Full details of the methodology can be obtained from the previously published analysis[27].

GDS score measurement

Geriatric Depression Scale-Long Form 30(GDS-LF30) was used to collect data on depressive symptoms, consisting of 30 depression related self-rating questions with simple 'yes' or 'no' options and a score ranging from 0 to 30. This scale was exclusively developed for screening and rating severity of depression in elderly and has shown very good criterion validity. When a cutoff score of 11 is used, it has a sensitivity of 84% and specificity is 95%[28]. We used the same cutoff value to differentiate between non-depressed and depressed (0–10=Not depressed, 11–30=Depressed). GDS scores were collected at baseline and at the end of the study. At baseline we also collected information about other associated variables such as level of education, previous history of depression, history of hypothyroidism, living status, smoking habits and alcohol consumption.

Genotyping

Genotyping was performed on DNA extracted from the subject's white blood cells using Puregene kit (Gentra systems) for ER- α SNP's and standard phenol/chloroform extraction procedure for VDR SNP's (BsmI- rs1544410 and TaqI- rs1544410). Genotype Coding for ER-alpha restriction sites was Pp for PvuII and Xx for XbaI. For VDR SNP's, Bb denotes BsmI and Tt denote TaqI. Uppercase and lowercase letters denoted the presence and absence of a restriction sites respectively. Polymerase chain reaction (PCR) was used to extract DNA and the products were digested using appropriate restriction endonucleases. The fragments were processed using gel electrophoresis, stained with ethidium bromide for clear visualization under UV light and photographed.

Biochemical measurements

Serum 25-hydroxy vitamin D (25 (OH) D) was assayed with a competitive protein-binding assay. Serum total estradiol, SHBG and serum total testosterone were measured in fasting baseline serum samples using RIA kits (Diagnostic Systems Laboratories, Webster, TX). The intra-assay co-efficient of variation for the assays were as follows: serum 25OHD 5.1 percent, estradiol 4.1 percent, SHBG 8.2 percent and testosterone 7.4 percent.

Statistical Methods and analyses

All analyses were performed using SPSS Version 19 (IBM SPSS Inc). Baseline characteristics were compared among four treatment groups by means of one-way ANOVA for continuous variables and by chi-square test for categorical variables.

For the baseline cross sectional analysis we categorized 25OHD level into vitamin D insufficient or sufficient based on a cut-off of 20 ng/ml and used chi-square test to find correlation with depression (yes/no). To compare genotype polymorphisms among depressed and non-depressed people we used chi-square tests and, to compare genotype polymorphisms and response to treatment (defined as difference between final GDS and baseline GDS score) we used linear regression. We used one-way ANOVA to find association between baseline depression and serum total estradiol, SHBG and total testosterone.

For the longitudinal analyses we used binary logistic regression analysis to determine the effect of HT and calcitriol on depression. The final GDS score was categorized into depressed or non depressed and was used as the dependant variable and the treatment group (placebo as reference) as the categorical variable in binary logistic regression. We also did a subgroup analysis on depressed people at baseline using one-way ANOVA to find the effect of treatment. The confidence intervals (CI) estimated for odds ratios of depression were calculated with 95% probability. The significance level was set to 0.05 for all analyses in our study. We performed the modified intent-to-treat analyses on 412 participants who came in for both baseline and final visit. Also we performed the longitudinal analysis on compliers (n=337).

RESULTS

A total of 489 participants were enrolled in this study. One subject was excluded because of new onset Paget's disease. All the participants completed the GDS questionnaire at baseline (n=488). At the end of the study 412 participants (85%) completed the GDS questionnaire and 76 women (15%) did not complete it (non-response) and 337 finished on active drug (compliers). Our study population was successfully randomized and the groups did not differ significantly from each other. Baseline characteristics are summarized in Table 1.

The mean age was 71.4(SD±3.6). Nineteen (4%) women were taking antidepressants at baseline but we found 57(12%) women had depression based on baseline GDS scores. There were 89(18%) women who were hypothyroid and 189(39%) were living alone. There were 199(41%) hysterectomized women and 289(59%) non-hysterectomized women. There were 57(12%) participants who were minimally educated.

Mean GDS score at baseline was 4.8(SD±4.6) and at 36 months it was 4.2(SD±4.2). Mean serum 25(OH) D was 31.3 ng/ml (SD±10.5). Mean serum total estrogen was 11.95 pg/ml (SD±5.07), mean SHBG was 147.47 nmol/liter (SD±67.7) and mean total testosterone was 0.23 nmol/liter (SD±0.11). There were 57 women with depression at baseline: Placebo 17 women, HT with calcitriol 10 women, HT 18 women, and Calcitriol 12 women. At final visit the number of women with depression decreased in all the groups regardless of intervention given: Placebo 11 women, HT with calcitriol 8 women, HT 14 women, and Calcitriol 9 women.

The distribution of ER- α (XbaI, PvuII) and VDR (BsmI, TaqI) genotypes in our study population followed the Hardy–Weinberg Equilibrium.

Intent-to-treat Cross sectional Analysis at baseline

Serum 25OHD levels and Depression: At baseline chi-square analysis between serum 25(OH) D and depression showed no significant correlation (X^2=0.944, p=0.331).

ER- α polymorphisms and depression: The chi square analysis showed no significant association between depression and ER- α polymorphisms XbaI and PvuII (X^2 =0.894, p=0.640, and X^2 =0.215, p=0.898 respectively)

VDR polymorphisms and depression: At baseline depression did not show any association with VDR polymorphisms BsmI and TaqI (X^2 =0.771, p=0.680, and X^2=0.901, p=0.637 respectively).

Total Estradiol, SHBG and Total Testosterone and depression: Serum total estradiol, SHBG and total testosterone level did not show any significant difference between depressed and non-depressed people at baseline (F=0.014, p=0.904; F=0.014, p=0.953 and F=1.561, p=0.212 respectively).

Intent-to-treat Longitudinal analysis

In the modified ITT analysis (n=412), we used binary logistic regression to find effect of intervention on depression and there was no effect of HT (OR 1.65; 95% CI 0.66–4.12; p = 0.277), calcitriol (OR 1.15; 95% CI 0.43–3.11; p = 0.772) or HT+ Calcitriol (OR 1.01; 95% CI 0.36–2.80; p = 0.979) on depression. (Table 2)

In sub-group analysis using one-way ANOVA, all the participants who were depressed at baseline shopwed a significant improvement in depression (final GDS-baseline GDS) when compared with non-depressed people (F=68.82; p=0.000). This improvement was seen in placebo and all treatment groups (figure 1). The response to treatment (defined as difference in final and baseline GDS scores) was not associated with ER- α and VDR polymorphisms. (beta=0.093, CI −0.337–1.350, p = 0.239 for XbaI; beta=−0.064, CI −1.171-0.491, p = 0.421 for PvuII; beta=0.044, CI −2.546–3.030, p = 0.865 for BsmI and beta=−0.015, CI −2.900-2.738, p = 0.955 for TaqI).

Complier Longitudinal Analysis

In compliers (n=337) the results remain unchanged and there was no effect of HT (OR 2.22; 95% CI 0.77–6.42; p = 0.140), calcitriol (OR 1.77; 95% CI 0.59–5.30; p = 0.305) or HT+ Calcitriol (OR 1.19; 95% CI 0.34–4.18; p = 0.776) (See Table 2).

DISCUSSION

The purpose of this secondary analysis was to see if HT and calcitriol either combined or individually had an effect depression in elderly postmenopausal women and to see if there was any relationship between depression and polymorphisms of ER- α and VDR. We believe that this is the first study to compare the combined and individual effects of HT/ET and calcitriol on depression longitudinally. The evaluation of association between ER- α, VDR genotype polymorphisms, estradiol, SHBG, testosterone and depression provides an insight for the future researchers.

It has been shown in several studies that estrogen has either a weak or no association with depression. Two large trials WHI (Women's Health Initiative) and WISDOM (The Women's international study of long-duration oestrogen after menopause) failed to demonstrate an improving effect of HT on depression. The Women's Health Initiative trial was unable to demonstrate a benefit of estrogen on depressive symptoms and effect[29]. In a recent double-blinded placebo controlled trial involving 3721 women between 50–69 ages,

it was shown that combined HT had no effect on depression[30]. Also in a study from three French cities (Three City Study), after evaluation of 4,069 postmenopausal elderly women by giving HT and following for four years authors could not find a protective effect of estrogen against the emergence of depressive symptoms[31]. Our results support these findings, since HT was showed no influence on depression. In contrast, a meta-analysis of the effect of HT on depressive mood by Zweifel et al suggested a moderate to large effect of HT on depressed mood[32]. However estrogen alone (ET) had effect but not when combined with medroxyprogesterone acetate (HT). In our analysis, women in estrogen only group were not influenced by treatment.

Depression is thought to be due to an alteration in serotonergic system although other neurotransmitters are also involved. Estrogen is known to have a modulating effect on all of these neurotransmitter pathways especially the serotonergic pathway[33]. In one study conjugated equine estrogen therapy improved mood in depressed postmenopausal women[34]. There is some data suggesting that progestins can antagonize the neuroprotective effects of estrogen[9]. However we saw no significant difference in the response to estrogen alone or combined with progestin.

The effect of vitamin D on depression in elderly population has not been studied extensively. Although few prospective studies demonstrated a relationship between vitamin D and depression but there exists a controversy. In a cohort study of 1155 participants older than 65yrs of age, low levels of serum 25OHD (<50 nmol/liter) were associated with depressive symptoms and the association was higher in women than men[35]. However in our study the baseline analysis did not show a relationship between baseline serum 25 (OH)D insufficiency (<20 ng/ml) and depression. At the end of our study there was no effect of vitamin D supplementation on depression.

Recently in a large randomized placebo controlled trial conducted by Sanders et al in Australia involving 2317 elderly women, annual high dose of vitamin D3 (500 000 IU) with three-year follow-up failed to prevent depressive symptoms[22]. In a cross sectional study by Jorde et al involving 441 obese men and women, it was shown that participants with serum 25(OH) D levels more than 40 nmol/liter were associated with low depression scores on the BDI scale but this study was unadjusted for the common confounders[20]. In another study on a small group of 21 elderly participants with secondary hyperparathyroidism not due to renal failure, they found that low serum 25-hydroxyvitamin D (50 nmol/liter) was associated with a lower depression score[36]. Recently evidence from WHI analysis of relationship between vitamin D intake from foods and supplements and depressive symptoms supports our finding that supplementation of vitamin D was not associated with depressive symptoms[37]. We could not find any significant relationship between serum 25 hydroxy vitamin D levels and depression.

Although several other studies demonstrated an association between low levels of serum 25OHD and major depressive disorder[38] and also between vitamin deficiency and low mood[19], long-term treatment in this study did not show an effect of calcitriol in postmenopausal women. No previous study has evaluated the combined effect of HT with calcitriol but no significant improvement in depression was observed in this study.

Genotypes can affect the response to treatment as found in the studies with regard to changes in lipids and bone density[39,23]. In one study by Malacara et al in 177 postmenopausal women, authors did not find a significant association between ER- α genotypes (PvuII and XbaI) and depression[24]. Another study reported increased risk of anxiety with ER- α polymorphisms but not depressive symptoms[25]. However in a case control study by Kim et al, they found a strong association between ER polymorphism and

depression in postmenopausal women[40]. Similarly in the Three City Study, Ryan et al found two polymorphisms of ER- α and one polymorphism of ER- β were associated with depression in women[15]. In our study we did not find an association between either ER- α or VDR genotype polymorphisms and depression.

Vitamin D responsive elements are present in the promoter regions of serotonin receptors and tryptophan hydroxylase receptors, both of which are known to be associated with depression[41]. In one study it was shown that VDR polymorphisms influence the susceptibility to depression in old age[26], but vitamin D levels were not measured which might have influenced the association. Our study showed no association between VDR polymorphisms and depression or the response to treatment. We recommend larger studies to confirm these genotype findings.

The strengths of this study are large postmenopausal population with 3 year follow-up, excellent validity of GDS LF 30 scale which is a powerful screening tool covering wide range of depressive symptoms, baseline adjustment to the known potential confounders. The unique strength of this study was combination effect of HRT and Calcitriol on depression. However all the data collected on depression were self-reported instead of clinical diagnosis. Recall bias may had an effect because of the age of the population. We had no data on socio-economic status, which is one of the known confounders. The finding that all the women showed improvement irrespective of intervention given might be due to the regression to mean (floor effect) as they have more chance for improvement compared to non-depressed people. In retrospect our study did not have sufficient numbers of depressed people with blood levels representative of moderate to severe vitamin D deficiency. Moreover larger studies will be required to confirm genotype association with depression because of low number of depressed people in our study.

CONCLUSION

In summary, neither HT nor calcitriol either individually or in combination showed a statistically significant effect on depression in elderly post-menopausal women. There was no evidence that ER- α and VDR polymorphisms were associated with depression or the response to treatment in elderly postmenopausal women.

Acknowledgments

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Fig. 1.
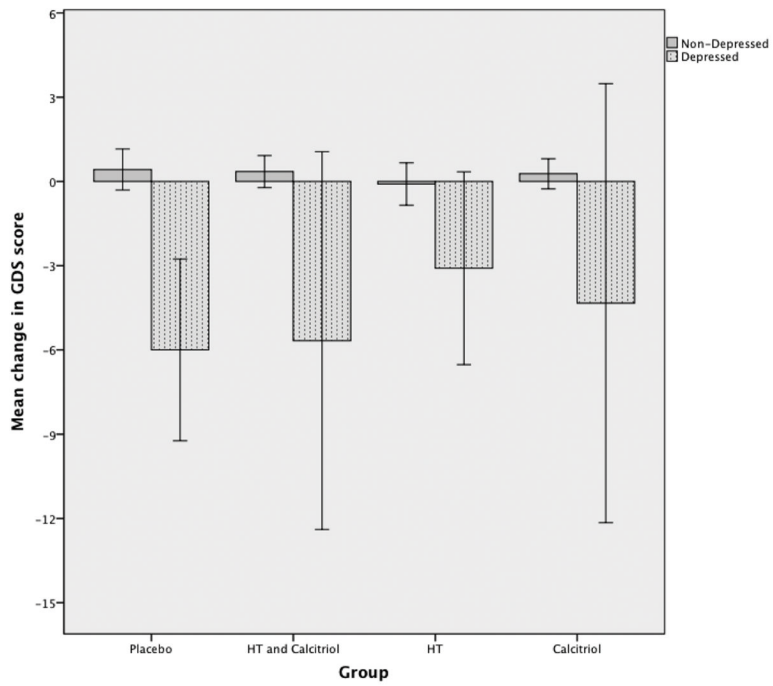Comparison of mean change in GDS scores in depressed and non-depressed people.
Error bars represent 95% C.I.
HT-Hormone Therapy with conjugated equine estrogens 0.625 mg/daily in hysterectomized women or combined with medroxyprogesterone acetate 2.5 mg/daily in women with intact uterus. Calcitriol - 0.25g twice daily.
Y-axis represents mean of difference between final GDS and baseline GDS.

Table 1

Baseline characteristics of the study subjects (n=488)

Variable	Value (All subjects n=488)	Placebo (n=1(n=123)	HT[a]+Calcitriol[b] (n=122)	HT (n=120)	Calcitriol (n=123)	P value[c]
Age in years:mean (SD[d])	71.4(±3.5)	71.1(±3.7)	71.4(±3.6)	71.4(±3.6)	71.8(±3.4)	0.536
BMI (kg/m²):mean (SD)	27.0(±4.8)	27.22 (±5.0)	26.7(±4.3)	27.5 (±4.6)	26.7(±5.4)	0.541
Education (n):						
Minimum	57	14	12	13	18	0.674
More than minimum	431	109	110	107	105	
Living (n):						
Living alone	189	43	47	50	49	0.744
Lining with others	299	80	75	70	74	
Hypothyroidism (n):						
No	399	100	98	99	102	0.952
Yes	89	23	24	21	21	
Antidepressant use (n):						
No	469	117	119	115	118	0.796
Yes	19	06	03	05	05	
Smoking (n):						
No	430	108	108	103	111	0.763
Yes	58	15	14	17	12	
Alcohol (n):						
No	325	83	84	81	77	0.741
Yes	163	40	38	39	46	
Baseline Depression (n)	57	17	10	18	12	0.295
Baseline GDS[e] Score: mean (SD)	4.8 (±4.6)	4.6(±4.5)	4.3(±4.2)	6.0(±5.0)	4.5(±4.5)	0.022
Final GDS Score: mean (SD)	4.2(±4.2)	4.0(±4.0)	4.0(±4.4)	5.1(±4.4)	3.9(±3.9)	0.100
Baseline serum 25-hydroxyvitamin -D, mean (SD), ng/ml	31.3(±10.5)	31.7(±11.0)	32.0(±11.6)	30.9(±9.9)	30.6(±9.4)	0.694
Serum total estradiol (pg/ml): mean (SD)	11.95(±5.07)	12.23(±5.23)	11.27(±4.55)	11.54(±4.72)	12.76(±5.63)	0.155
Serum SHBG (nmol/liter): mean (SD)	147.47(±67.7)	142.78(±66.3)	159.53(±74.5)	142.27(±65.5)	145.74(±63.7)	0.235
Serum total testosterone, mean (SD), ng/ml	0.23(±0.11)	0.23(±0.11)	0.23(±0.11)	0.24(±0.10)	0.24(±0.12)	0.688

Xbal[f](n=337)

Variable	Value (All subjects n=488)	Placebo (n=1(n=123)	HT[a]+Calcitriol[b] (n=122)	HT (n=120)	Calcitriol (n=123)	P value[c]
xx	132	33	29	36	34	
Xx	157	41	43	40	33	0.212
XX	48	20	7	9	12	
PvuII[g](n=338)						
pp	96	26	25	20	25	
Pp	171	45	40	49	37	0.675
PP	71	24	14	16	17	
BsmI[h](n=362)						
bb	141	44	33	32	32	
Bb	169	46	40	42	41	0.898
BB	52	12	11	16	13	
TaqI[i](n=362)						
tt	51	12	10	16	13	
Tt	171	45	41	43	42	0.774
TT	140	45	33	31	31	

[a] Hormone Therapy with conjugated equine estrogens 0.625 mg/daily in hysterectomized women or combined with medroxyprogesterone acetate 2.5 mg/daily in women with intact uterus

[b] Calcitriol 0.25g twice a day

[c] One-way ANOVA was used for comparing continuous variables and Chi-square test for categorical variables

[d] Standard deviation

[e] Geriatric Depression Screening score

[f,g] Estrogen receptor -alpha single nucleotide polymorphisms–numbers indicate frequencies

[h,i] Vitamin D receptor single nucleotide polymorphisms– numbers indicate frequencies

Table 2

Factors affecting depression: Binary Logistic Regression Model

Variable	Standard Error	*p* (sig.)	OR	95% Confidence Interval	
				Lower	Upper
Modified ITT[a] analysis (n=412)					
Placebo (reference)	-	-	-	-	-
HT[c]+Calcitriol	.519	.979	1.014	.367	2.805
HT	.465	.277	1.657	.666	4.120
Calcitriol	.505	.772	1.158	.430	3.117
Baseline GDS[b] score	.398	.000	10.699	4.902	23.352
Compliers analysis (n=337)					
Placebo (reference)	-	-	-	-	-
HT[c]+Calcitriol	.666	.776	1.199	.343	4.183
HT	.588	.140	2.224	.769	6.428
Calcitriol	.605	.305	1.774	.594	5.303
Baseline GDS score	.513	.000	12.368	5.061	30.225

[a]Intent to treat

[b]Geriatric Depression Screening score

[c]Hormone therapy with conjugated equine estrogens 0.625 mg/daily in hysterectomized women or combined with medroxyprogesterone acetate 2.5 mg/daily in women with intact uterus