ORIGINAL ARTICLE

VITAMIN B12 ADMINISTRATION FACILITATES THE ANTI-PSYCHOTIC AND PAIN-RELIEVING EFFECTS OF QUETIAPINE, IN THE ALZHEIMER PATIENTS WITH PSYCHOTIC SYMPTOMS

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Background: Psychotic symptoms in Alzheimer's disease (AD) patients are a problem in medicine. The efficacy of the vitamin B12 on the treatment of the psychotic symptoms of the AD patients in the association with antipsychotic drugs Quetiapine and Risperidone, was evaluated in this Study. **Methods:** The effects of vitamin B12 along with two other drugs were studied on the Mini–Mental State Examination (MMSE), Clinical Global Impression (CGI), Brief Psychiatric Rating Scale (BPRS) and pain Visual Analogue Scale (VAS) in 47 AD patients with psychotic symptoms, including 4 groups, psychotic AD patients treated with Risperidone, Risperidone plus vitamin B12, Quetiapine and Quetiapine plus vitamin B12. **Results:** The results showed that Quetiapine improved all of the psychotic criteria, while Quetiapine plus vitamin B12 had better results on BPRS after 2 weeks, VAS score and MMSE. Risperidone also improves all of the criteria except MMSE and drug efficacy index, while, vitamin B12 neutralize the effects of the Risperidone on the BPRS, VAS, and severity of illness. **Conclusions:** Due to these results, Quetiapine is the preferred antipsychotics drug and Vitamin B12 plays an effective role in treatment as an adjunct therapy.

Keywords: Psychosis; Alzheimer disease; Vitamin B12; Quetiapine

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INTRODUCTION

Alzheimer disease (AD) is an aging-associated disorder, which is considered the most common dementia disease. Almost, AD is associated with significantly reduced ability and cognitive function.[1] It is estimated that the AD prevalence rate is increasing to 1 in 85 subjects until the year 2050.[2,3] One of the challenging items in AD patients is the control of agitation and psychosis with a long list of new antipsychotics which most of which are in the third phase of their approval study.[4–7]

The current potential treatment protocol for Behavioural and psychological symptoms of dementia (BPSD) are aimed to increase and decrease the production of neurotransmitters like acetylcholine, and dopamine/serotonin, respectively.[8] Therefore, antipsychotic drugs, such as Risperidone and Quetiapine, are designed to decline AD psychotic symptoms via the mechanism. Additionally, psychotic symptoms are common in patients with dementia (85%), and pain is thought to be an important underlying factor. Pain has previously been associated with agitation, and pain treatment has been shown to ameliorate agitated symptoms.[9] So far, the association between pain and psychosis and the effects of pain treatment on psychotic symptoms is unclear. In many studies, there was a paradox about the aetiology of psychotic symptoms of dementia and its underlying causes.[10]

However, the protocols, using Risperidone and Quetiapine, are unable to overcome AD pain in psychotic patients.[11] Thus, the current investigations are aimed to introduce safe methods to decrease the psychotic Alzheimer patient's pain. Previous investigations showed

that vitamin B12 may be considered as a component to decrease pain.[12] Pain is an important cause of agitation and psychosis in dementia patients, so pain treatment even with narcotics could reduce agitation and psychosis in them.[13] Thus, vitamin B12 and its combination, as a pain reducer, with antipsychotic drugs, including Risperidone and Quetiapine, may be associated with amelioration of AD pain and psychosis respectively.

Therefore, this clinical trial study was aimed to explore the vitamin B12 effects on the psychotic symptoms and pain of the psychotic AD patients, who received antipsychotic drugs, Risperidone and Quetiapine.

MATERIAL AND METHODS

This study was a parallel randomized clinical trial designed to explore the effects of vitamin B12 along with two antipsychotic drugs on the Mini-Mental State Examination (MMSE), Clinical Global Impression (CGI),Brief Psychiatric Rating Scale (BPRS)and Visual Analogue Scale (VAS) in 47 participants, including 4 groups with allocation ratio 1:1. Accordingly, the groups were as follow: Group 1: Psychotic AD patients who were treated with Risperidone, Group 2: Psychotic AD patients who were treated with Risperidone and vitamin B12, Group 3: Psychotic AD patients who were treated with Quetiapine and Group 4: Psychotic AD patients who were treated with Quetiapine and vitamin B12.

We used 1000 microgram vitamin B12 injection monthly for B12 user groups.

The participants were selected from an elderly Iranian population (over 65 years old) who were referred to the neurologists in Rafsanjan city. First of all, Alzheimer patients with major neurocognitive impairment as in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM5) and National Institute on Aging (NIA) and the Alzheimer's Association (AA), [14] with at least two cognitive abilities involvement like MMSE less than 20, BPRS between 30–70 were selected after laboratory exam and Radiologic studies ruled out other causes of dementia.

Inclusion criteria of cases:

1-MMSE: our cases should have MMSE ≤ 20.

2-The BPRS score should be between 30-70.

3- The age of them should be above 65 years.

In the groups treated with risperidone, it was administered at a dose of 0.5 mg overnight, gradually increasing to 1 mg and 2 mg, respectively, during subsequent follow-up visits. In the groups treated with Quetiapine, the dose was administered 12.5 mg overnight and increased to 25 and 50 mg depending on the patient's condition. If the patient needs further intervention and adjunctive treatment based on the patient's condition or family statements, the patient will be excluded from the study.

Exclusion criteria for our study were the use of antipsychotic drugs, schizophrenic symptoms, primary psychotic disorders, delirium, other dementia disorders, psychosis following drug or drug abuse or dementia disorders, other underlying severe medical disorders or cardiac disease, patients who need hospitalization, patients at risk of suicide.

Based on the pilot study and using the relevant formulas and parameters below, the minimum sample size of 12 people for each of the 4 groups ((Risperidone / Risperidone + B12 / Quetiapine / Quetiapine + B12) was obtained, taking into account that the four groups in the study. There, for each group, 20 people (n * √ (4-1)) and a total of 80 people were determined.

$$n = \frac{\left(\sigma_1^2 + \sigma_2^2\right)\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2}{\delta^2}$$

$$N = n * \sqrt{k-1}$$

3.4700 ← δ (size of difference of clinical importance) = $\mu 1 - \mu 2$

Significance level =0.0500

Power = 0.80 m1 = 18.3300 m2 =21.8000

sd1 = 3.2000 sd2 =2.5000

MMSE and CGI are the scales that are used to diagnose dementia,[15] and mental disorders symptom severity, treatment response/efficacy,[16] respectively. Additionally, BPRS and VAS are the other scales for the assessment of psychiatric symptoms[17] and pain levels,[18] respectively.

The AD patients suffering from severe immune-related diseases such as insulin-dependent diabetes, thyroid, cardiovascular, infectious, and kidney/liver disorders have been excluded from the clinical trial.

The patients under treatment with anti-inflammatory/immunosuppressant drugs (except acetylsalicylic acid) have also been excluded from the project. Accordingly, at the start time of the study, 80 participants were entered into the trial, and then due to the excluding criteria, 33 cases were excluded or not continued the trial, and 47 cases remained in the study. (Figure-1)

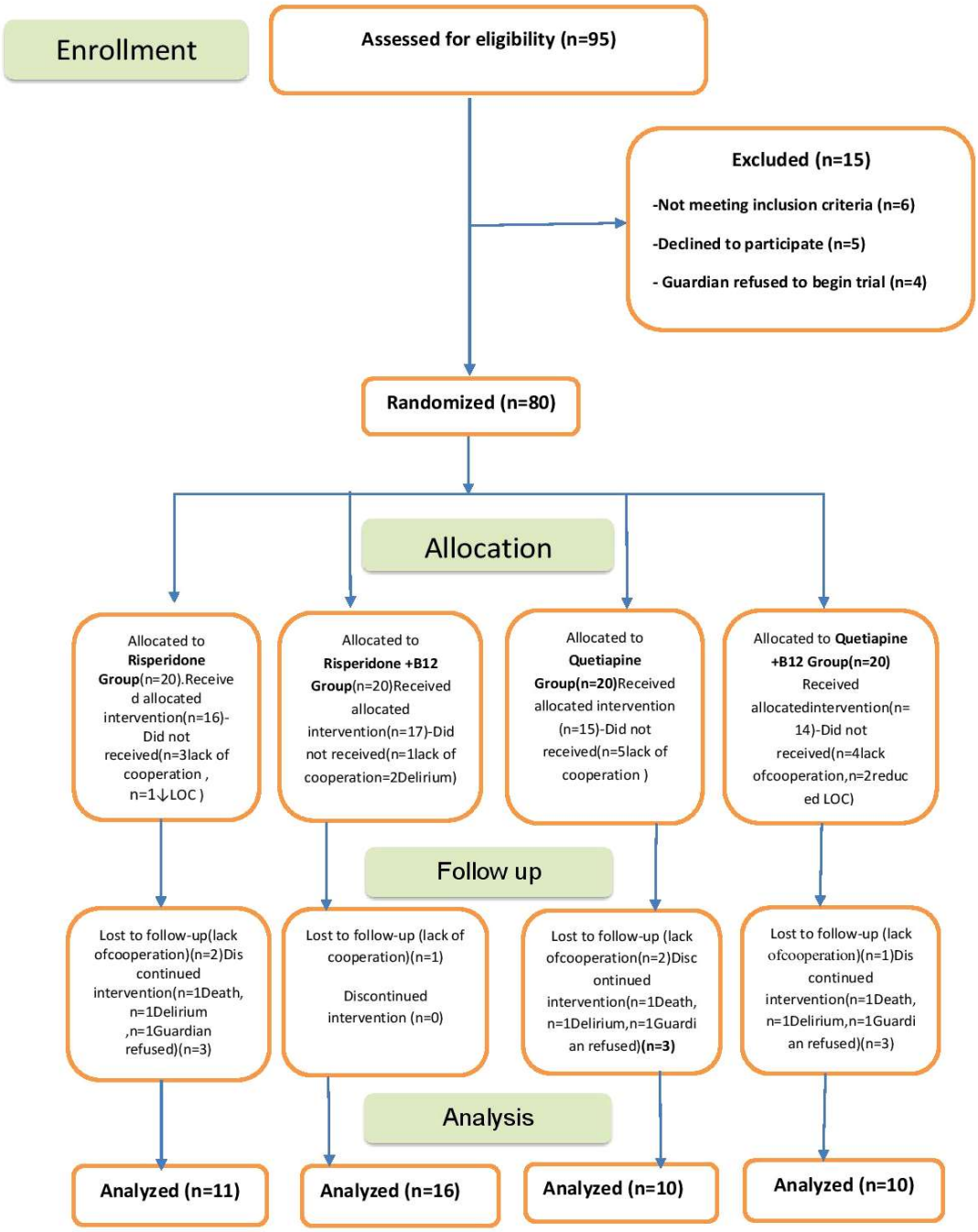

Figure-1: Design of study

MMSE, CGI, BPRS, and VAS scales among the groups were recorded before treatment, two weeks after treatment and 8 weeks after treatment using the standard questionnaires which were described previously.[18–21] The CGI scores were evaluated in details as the severity of illness, general improvement rate and drug efficacy index.

Evaluation of the above tests and drug prescribing are performed by two clinicians separately. Serum levels of blood vitamin B12 are measured and compared at the beginning for ruling out other causes of dementia. Patients who met the eligibility requirements were randomized to receive one of the four treatments via a random number table of simple randomization.

Of all participants, in follow-up period three patients died during the study and twelve other patients were excluded from the study for various

reasons (Figure-1). Finally, 47 patients remained in the four groups and remained in the trial for eight weeks. Those excluded from the study were classified as one man and two women in dead patients. Four people dropped out due to drug complications and refused to participate in the project, which included three men and one woman. Seven women and four men either arbitrarily withdrew the drug, or fellows refused further interviews.

This clinical trial was registered at the Iranian Registry of Clinical Trials, (IRCT) number: (Code: IRCT201501101061N18) and the Ethical Board of Rafsanjan University of Medical Sciences (Code: IR.RUMS.REC.1394.219) and have approved the project protocol. The patient's guardians filled out the written informed consent form before introduction to study.

Statistical analysis

Data was analysed using SPSS software version 16 (v16; SPSS Inc., Chicago, IL, USA). The normality of main variables was assessed and confirmed by Shapiro-Wilk and Kolmogorov-Smirnov tests and z-scores of data skewness and kurtosis. The differences of BPRS, CGI, MMSE, and VAS values between patient groups and time intervals inside each group were evaluated using repeated-measures ANOVA with a Greenhouse-Geisser correction, One-way ANOVA, and paired t-test. Fisher's exact test showed that the distribution of gender in the groups studied, differences were not statistically significant (p=0.417). A P-value less than 0.05 was considered significant.

RESULTS

The results from Shapiro-Wilk and Komogorov-Smirnov tests revealed that the data were distributed normally, hence, the parametric tests were used to compare raw data.

Mean age of patients was 80.70±7.75 and 27 female and 20 male patients participated in our study. Accordingly, the results showed that the groups were properly matched regarding age (p=0.332) and sex (p=0.417). The demographic characteristics of our cases are shown in table-1.

The statistical analysis demonstrated that the BPRS score was significantly decreased after 8 weeks treatment with Risperidone when compared to the before treatment (p=0.035). However, the BPRS score was not changed significantly in the group that has treated with Risperidone and vitamin B12 (p=0.140). The BPRS score was also decreased after 2 weeks of treatment (p=0.015) and 8 weeks (p=0.040) when compared to the before treatment with Quetiapine. Treatment with Quetiapine and vitamin B12 simultaneously led to a decrease in the BPRS score significantly after 2 weeks treatment (p=0.039), but not after 8 weeks treatment. Figure-2 shows the BPRS scores among the groups which have been treated with Risperidone, Quetiapine, Quetiapine plus vitamin B12, and Risperidone plus vitamin B12.

Although, treatment with Risperidone (p=0.235) and Quetiapine plus vitamin B12 (p=0.190) did not alter the MMSE score, Risperidone plus vitamin B12 (p=0.033) and Quetiapine (p=0.035) significantly increased MMSE scores (Figure-3).

As it is illustrated in figure 4, there are significant differences in VAS score between before and 8 weeks after treatment of the patients with Risperidone (p=0.017), Quetiapine (p=0.05) and Quetiapine plus vitamin B12 (p= 0.023). However, treatment with Risperidone plus vitamin B12 was not associated with decreased VAS score significantly (p=0.863).

Treatment with all components, including Risperidone, Risperidone plus vitamin B12, Quetiapine and Quetiapine plus vitamin B12 significantly increased the CGI scores (p< 0.001, figure 5).

The CGI details regarding the severity of illness, general improvement rate and drug efficacy index demonstrated that Risperidone (p<0.001), Quetiapine (p<0.001) and Quetiapine plus vitamin B12 (p<0.001), but not Risperidone plus vitamin B12 (p=0.259), significantly decreased the severity of illness in the patients (Figure-6).

While Risperidone (p<0.012), Risperidone plus vitamin B12 (p<0.001) and Quetiapine (p=0.003), but not Quetiapine plus vitamin B12 (p=0.193), significantly decreased general improvement rates after 8 weeks when compared to results obtained from 2 weeks (Figure-7). (Supplementary)

In the case of drug efficacy index, Quetiapine was the unique component that led to decrease drug efficacy index scores after 8 weeks when compared to results obtained from 2 weeks (p=0.045, figure 8). (Supplementary)

The statistical analysis revealed that there were no significant differences among the groups before treatment regarding BPRS (p=0.464), MMSE (p=0.958), VAS (p=0.871), severity of illness (p=0.547), global improvement rate (p=0.887) and drug efficacy index (p=0.124). BPRS (p=0.685), MMSE (p=0.847), VAS (p=0.906), severity of illness (p=0.910), global improvement rate (p=0.113) and drug efficacy index (p=0.374) were not also differed among the groups after 2 weeks treatment. The same results also were obtained regarding treatment after 8 weeks (BPRS (p=0.710), MMSE (p=0.918), VAS (p=0.465), severity of illness (p=0.951), global improvement rate (p=0.899) and drug efficacy index (p=0.290)).

Table-1: Some demographic characteristics of our AD patients before clinical trial

Characteristic / Group	Sex*	Age *	MMSE(Mean)	BPRS (Mean)
Group1(Risperidone)	4F,7M	79.54±7.35	10.18±0.70	54.45± 6.10
Group2(Ris+B12)	10F,6M	81.52±6.96	11.00±0.80	46.50± 5.45
Group3(Quetiapine)	7F,3M	78.56±7.90	10.63±0.79	47.75± 5.35
Group4(Que+B12)	6F,4M	81.20±7.20	11.50±0.65	56.10± 6.49

*No significant difference in sex between groups. (p=0.417). *No significant difference in age between groups. (p=0.332)

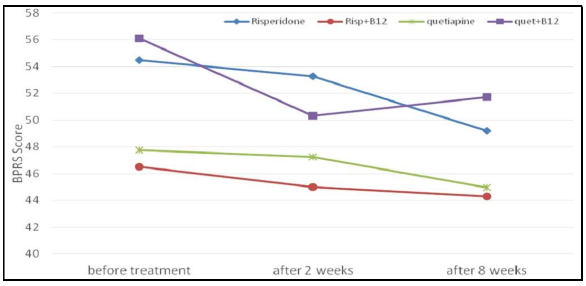

Figure-2: BPRS score in trial groups

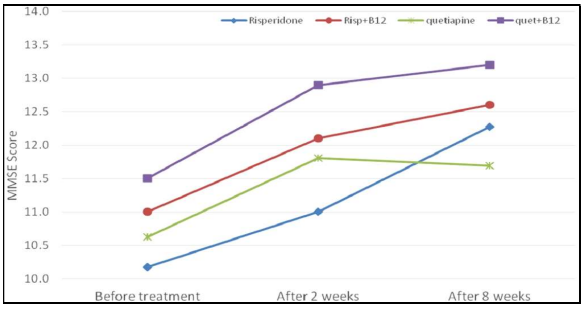

Figure-3: MMSE score in trial groups

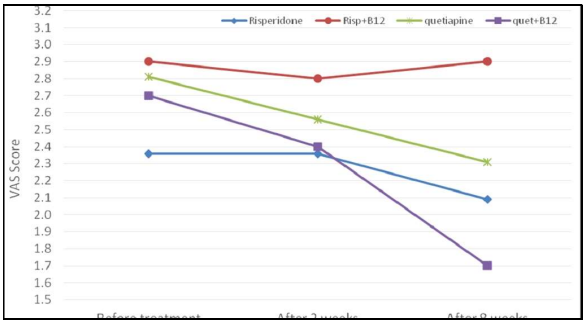

Figure-4: VAS score in trial groups

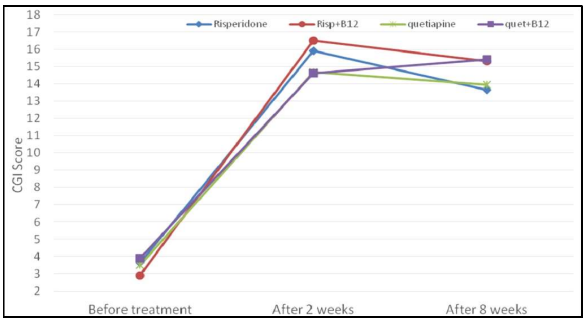

Figure-5: CGI Score in trial groups

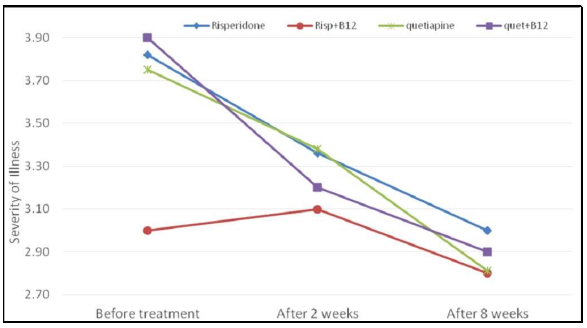

Figure-6: Severity of Illness Score in trial groups

DISCUSSION

This study was designed to evaluate the effects of two drugs, Risperidone and Quetiapine, and their combinations with vitamin B12 on the psychotic symptoms and pain of AD patients.

It has been demonstrated that the patients who suffer from Alzheimer, may be associated with BPSD. [8]Nowadays, researchers are investigating the new treatment protocols to overcome the psychological symptoms in the patients.[22,23] In a study, sodium valproate was used as a treatment for BPSD of AD patients in parallel to Quetiapine.[22]

Antipsychotic drug doses in our cases are flexible and the range of doses is based on the patient's response to Risperidone and Quetiapine. It was appeared to be more effective than the fixed-dose model for all patients.

First of all, antipsychotic effects of these two drugs have been studied in many articles. Zhu (2012)[23] showed the similar antipsychotic effect of Risperidone and Quetiapine on patients but Quetiapine has fewer side-effects in this study. In our study Quetiapine had a better effect on lowering BPRS score although both drugs had valuable effects.

Vigen (2011) found that one year's use of anti-psychotics' drugs could reduce MMSE and other cognitive scores.[24] Our study with 8 weeks follow-up could not compare with Vigan's study with one-year follow-up but was similar to another study for its duration of the study.[23] In our study, Quetiapine use alone showed a small reduction in cognitive scores in 8 weeks after its use, that is like Vigen study results , which compensated in another group of our study in which vitamin B12 is used simultaneously in it.

The results showed that Quetiapine was the unique component that improves all of the evaluated criteria, including BPRS, MMSE, VAS, the severity of illness, global improvement rate, and drug efficacy index in the beginning weeks of the study. Using vitamin B12 in association with Quetiapine led to facilitate the effects of Quetiapine on reducing VAS score and BPRS, as is illustrated in figure-3, vitamin B12 reduced VAS, in the cases treated with Quetiapine, this difference was not significant. The BPRS score significantly reduced after 2 weeks of treatment with Quetiapine and vitamin B12. There are other studies with opposite results about improving cognitive scores.[24] This difference could be due to the use of vitamin B12 in our study.

In 2007 Stroup studied risperidone, quetiapine, and olanzapine and found valuable results on psychotic symptoms of schizophrenic patients in all of them. Quetiapine and olanzapine were more effective than risperidone. There was no side–effect on cognition after six months of treatment.[25,26]

The results also demonstrated that Risperidone had no effects on the MMSE, as the dementia criteria, and drug efficacy index. Due to the results which showed no differences between groups regarding the variables before treatment, it may be concluded that Risperidone is not applicable as well as Quetiapine. Interestingly, although vitamin B12 improved the effects of Risperidone to reduce MMSE scores, it neutralized the effects of Risperidone on the BPRS, VAS and severity of illness.

Collectively, it appears that vitamin B12 may be suitable to use in association with Quetiapine to treat psychotic Alzheimer patients. However, our previous investigations revealed that vitamin B12 can modulate production of some pro-inflammatory cytokines which participate in the pathogenesis of inflammation in the Alzheimer patients,[27] but it was unable to increase the efficacy of Risperidone and Quetiapine to reduce expression of scavenger receptor, CD68, on the monocytes[28].

In another double-blind study of aging people older than 70-year-old, using 500 microgram vitamin B12, 0.8 -gram folic acid and 20 mg vitamin B6 with decrease of blood homocysteine, reduced brain atrophy, and improved cognitive function were detected in comparison to the control group who took a placebo on the other hand.[29] Our study showed that B12 could improve MMSE score in Quetiapine and risperidone user patients.

There are many studies about vitamins/Neutraceucila formulation effect on cognition in AD patients. Li *et al* studied the role of vitaminB12, plasma total homocysteine, folate ,cholesterol, and triglyceride level in AD and found that only LDL cholesterol level is inversely related to cognitive performance.[30] Yang *et al* on the other hand in a meta-analysis study had not found a relation between Vitamin D deficiency and AD.[31] Inapposite Annweiler *et al* according to many studies before, accepted the role of vitamin D supplement as a cause of delaying AD onset in aging.[32] Gou *et al* found folate-vitamin B12 attenuation effect on tau-hyperphosphorylation induced by Hyper-homocysteinemia (Hhcy) in Hhcy rats models.[33] Moretti *et al* conducted that folate and vitamin D deficiency along with Hhcy are associated with dementia more in vascular dementia than AD.[34] In a review article about Shilajit and the effect of folate and complex B vitamins, there was evidence in favour of protect effect of these neutracecila on cognition deterioration of AD patients.[35] All of these investigations are more or less in favour of the protective effect of vitamins on cognition of AD patients especially vitamin B12 that our study showed beneficence of its use in AD patients.

Although, some studies reported that Risperidone and Quetiapine had no effects on the improvement of psychotic symptoms of the psychotic Alzheimer patients,[11] and in some cases were associated with worsening the symptoms[36,24]. Several investigations demonstrated that the effects of the anti-psychotics' drugs will be showed after 7–8 weeks of treatment.[37,38] In another study Quetiapine was used in low dose for delirium prevention in critically ill patients. This study approved the use of Quetiapine for a shorter period of delirium and faster weaning from ventilator.[39]

On the other hand, we could not ignore complications especially reported with Quetiapine that make it use with caution and control.[40]

It is in association with our results, which showed that the variables were improved after 8 weeks of treatment when compared to a pre-study condition in several cases.

There are limitations in our study including inadequate cooperation of patients' guardian for medication, lower number of patients participating in this project, higher risk of complications during treatment, problems in the follow-up of patients in the second and eighth weeks after the beginning of the trial.

CONCLUSION

Finally, the results of the current study showed that Quetiapine is a suitable antipsychotic drug and vitamin B12 facilitates the antipsychotic effect and relieving pain efficacy of it.

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Conflict of Interest: There is no conflict of interest to declare.

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AUTHORS'S CONTRIBUTION

AV: Concept, design, definition of intellectual content, literature search, manuscript preparation. AMA: Design, literature search, manuscript preparation, manuscript editing and manuscript review. MH: data acquisition. NJ: Data acquisition. MN: definition of intellectual content, literature search. MZB data analysis, statistical analysis. SMH: Definition of intellectual content, literature search, clinical studies, data acquisition. MM, AR, MA and PN: Data acquisition.

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