Effect of antidepressants on various periodontal parameters: A case–control study

Afshan Bey, Syed Saeed Ahmad,1 Suhail Ahmed Azmi,2 Sameena Ahmed3

Abstract:
Background: Various medications are used in the treatment of chronic systemic diseases that affect the periodontium. Antidepressants in mentally depressed patients are prescribed for a long term, but their effect on the periodontium has not been studied adequately. A case–control study was conducted to know the effect of two commonly prescribed antidepressants – venlafaxine (serotonin–norepinephrine reuptake inhibitor [SNRI]) and fluoxetine (selective serotonin reuptake inhibitor [SSRI]). These drugs have been shown to possess anti-inflammatory properties but do not protect the periodontium from insults caused by these medications, which are significantly associated with the presence of destruction of the periodontium. The aim of this study was to clinically evaluate the effect of antidepressants on various periodontal parameters. Materials and Methods: The study sample consisted of 182 depressed patients divided into three study groups: Group I – the control group diagnosed as depressed on the first visit, Group II – depressed patients taking fluoxetine 20 mg/day, and Group III – patients taking venlafaxine 75 mg/day. Patients in Groups II and III were on isolated antidepressant medication at least for a period of 3 or more months. Mental depression in patients was assessed with the Patient Health Questionnaire-based Hamilton Depression Rating Scale with scoring of ≤16. All the depressed patients were assessed for periodontal health on the basis of the clinical periodontal parameters. Results: The commonly prescribed antidepressants such as fluoxetine and venlafaxine do not protect the periodontium from destruction in spite of possessing anti-inflammatory properties; therefore, these drugs may be considered as a risk factor for periodontal health. The comparative periodontal indices on nonusers of antidepressants or control group (Group I), users of SSRI (fluoxetine) (Group II), and users of antidepressants-SNRI (venlafaxine) (Group III) showed increased periodontal parameters, especially debris index (DI), calculus index (CI), gingival index (GI), periodontal pocket depth (PD), and loss in clinical attachment level. There was no significant difference for CI and GI, probing PD, and clinical attachment levels except DI which was significantly different (P ≤ 0.001). Conclusion: The depressed patients receiving fluoxetine or venlafaxine should be regularly evaluated for periodontal health status as these drugs are risk factors for normal periodontal tissues. Further, these medications did not protect the periodontium from periodontal inflammation, although possessing anti-inflammatory properties.

Key words:
Antidepressant medications, attachment loss, clinical periodontitis, fluoxetine, Hamilton Depression Rating Scale

INTRODUCTION

Periodontitis is a multifactorial disease, which involves cellular and biochemical events for its progression and is characterized by a cascade of events that lead to loss of supporting periodontal tissues and the alveolar bone. These steps involve alteration in host response and behavioral and systemic risk factors. This disease is peculiar in the term that different individuals are affected by the same disease, but the progression is governed by different mechanisms. Various hormones and enzymes have been attributed to these changes in one individual, whereas they may be different for a different individual. Various studies in the past have shown that stress and depression also affect the periodontal tissues by behavioral and physiological mechanism in a manner similar to various diseases, like other diseases, besides that a large number of medicines are available to treat a variety of diseases which compromise the dental health of the patients. Some of these medicines have an adverse impact on the periodontium, and a definite interaction is also seen. Various anticonvulsant and...
antihypertensive calcium channel blockers like cyclosporine and nifedipine respectively have been attributed to gingival overgrowth, while drugs like immunosuppressant’s influences the response of gingival and periodontal tissues to bacterial plaqu. Corticosteroids, despite possessing anti-inflammatory and immunosuppressive properties, have not been used in the management of periodontal diseases so far. Further, it has been observed their long-term systemic use does not influence the extent of periodontal disease. Drug-induced bone marrow depression is a rare complication but has been shown to affect the periodontal tissue.[1]

Depression affects the regulatory mechanism within the brain and in fact dysregulates it with effect on the limbic system. Consequently, the immune response of the body is also altered leading to the development and progression of periodontal disease.[10] Although the chief etiological factor of periodontitis is bacteria present in the plaque biofilm, this initiates the immune response of the body to susceptible host bacteria which is basically responsible for the tissue breakdown and disease progression.

Depression is a chronic illness and is usually treated by different antidepressant medications which are given on a long-term basis. These drugs have been shown to possess anti-inflammatory properties and improve the immunity of the individual.[5-7]

However, the literature is scarce on their role on the periodontium, and it is important to evaluate the extent of periodontal affliction in depressed patients, if any. The present study was conducted with the aim to clinically evaluate the effect of antidepressants on various periodontal parameters in patients on antidepressant therapy; familiarity with the patient’s medical history, current prescriptions, and general indicators of depression could alert the dentist to possible problems and possibly facilitate an appropriate referral for evaluation of the depressive symptoms with satisfactory treatment outcomes.

Commonly used antidepressant such as fluoxetine does not inhibit norepinephrine and dopamine reuptake at therapeutic doses, but delays the reuptake of serotonin, and also persists longer when it is released. In large doses, it induces a significant increase in synaptic norepinephrine and dopamine. They produce antidepressant action at supratherapeutic doses (60–80 mg). This effect may be mediated by 5HT receptors which are inhibited by higher concentrations of fluoxetine.[8]

In addition to its main pharmacological antidepressive properties, it possesses a significant anti-inflammatory activity by reducing prostaglandin E2 concentration and increasing production of anti-inflammatory cytokine interleukin.[9]

Venlafaxine is an antidepressant belonging to serotonin–norepinephrine reuptake inhibitor (SNRI).[1,2] It acts by inhibiting primarily the reuptake of serotonin and noradrenaline and only partially the dopaminergic uptake. This drug increases the concentration of serotonin and norepinephrine in the body and brain tissues. This drug is basically used in the treatment of depressive disorders, anxiety disorders, panic disorders, and social phobia. At low doses, i.e., 150 mg/day, venlafaxine acts on serotonergic transmission; at moderate doses (>150 mg/day), it acts on serotonergic and noradrenergic systems; and at high doses (>300 mg/day), it also affects serotonergic and noradrenergic systems and dopaminergic neurotransmission. Venlafaxine (SNRI) is a commonly used antidepressant. Further, it enhances serotonin and noradrenaline concentrations, reduces anxiety and depression, and suppresses the peripheral inflammation.

**MATERIALS AND METHODS**

**Study design and sample selection**

This case–control study was performed at the Department of Psychiatry and Department of Periodontics. The study was approved by the Institutional Ethical Committee. Only those patients who attended the Psychiatry Outpatient Department (OPD) and agreed to participate in the study were included. Medical and dental history was taken, and the findings were recorded on specially designed format. All the participants in the study were assessed for the presence and severity of depression under the supervision of a psychiatrist. Only those patients were selected for the study with a HAM-D score more than 16 and were diagnosed as cases of moderate-to-severe depression.[10]

**Inclusion and exclusion criteria for selection of patients**

**Inclusion criteria**

1. Only adult patients (age range: 30–60 years)
2. Patients suffering from moderate-to-severe depression
3. Patients receiving single drug fluoxetine or venlafaxine for a period of 3–6 months
4. Individuals presenting at least with twenty teeth.

**Exclusion criteria**

1. All such patients who were either medically compromised or receiving multidrug therapy for the depression
2. Smokers, tobacco chewers, or any other such habits
3. Pregnant and lactating ladies
4. Patients who received periodontal therapy within 6 months
5. Patients on antibiotics, anti-inflammatory therapy, or vitamin/nutritional supplements for the past 6 months
6. Patients who had undergone any surgery or any other treatment in the past 6 months.

**Study groups**

The patients were divided into three groups:

- **Group I – Control**: Individuals reported for the first time in the psychiatry OPD and were diagnosed as mentally depressed patients by a psychiatrist
- **Group II – Patients taking fluoxetine** (20 mg/day for 3–6 months)
- **Group III – Patients taking venlafaxine** (75 mg/day in divided doses for 3–6 months).

**Study methodology**

Dental examination was done with the assistance of a periodontist in the Psychiatry OPD, Jawaharlal Nehru Medical College, under the standard protocol for examination of a dental patient. Probing pocket depth (PPD) and clinical attachment loss (CAL) were measured using a mouth mirror and Williams periodontal probe to assess the periodontal
status. Probing depths were recorded at four sites per tooth in six indexed teeth (maxillary right first molar, maxillary left central incisor, maxillary left first molar, left mandibular first molar, left mandibular central incisor, and right mandibular first molar), rounded up to the nearest millimeter. The healthy controls were not on any kind of medication or dietary restrictions.

The following indices were recorded:
1. Oral hygiene index ([11]) (OHI; Greene and Vermillion, 1964)
2. Gingival index ([12]) (GI, Loe and Silness, 1963)
3. Probing PD (PPD)
4. Clinical attachment level (CAL).

The results of the study were statistically analyzed with statistical program SPSS (Statistical package for social sciences) version 15.0 statistical analysis software, common syntax reference. 233, south wacker drive, Chicago. The values were presented in for of number, percentage, mean and standard deviation.

**RESULTS**

A total of 182 individuals were included in the study were fulfilling the selection criteria. The control group (Group I) consisted of 59 individuals, Group II (fluoxetine group) consisted of 62 patients, and Group III (venlafaxine group) consisted of 61 patients.

Table 1 presents the demographic parameters of participants in study Groups I, II, and III. These groups did not show any statistically significant difference between each other.

Table 2 demonstrates the comparative simplified OHI (OHI-S) between the control and the study groups. There was no statistically significant difference ($P > 0.05$) in study Group I and the study Group II. OHI-S which includes debris index (DI) and Calculus index (CI) projects the overall hygiene in an individual or group.

**DISCUSSION**

Depression is a commonly diagnosed disorder in the psychiatric clinics and its causal relation with periodontitis is a matter of concern to researchers. Genco et al. (1999) and Vettore et al. proposed their theory that behavioral changes led to periodontal disease and presented a model to explain the modulation of the immune system through hypothalamic–pituitary–adrenal (HPA) axis and sympathetic-adrenal medullary axis pathway. Further, it has been recognized that psychological stress or depression activates the inflammatory response, both in brain and peripheral tissues. Stress-induced activation of immune response has been well studied, and it has been found that its activation involves both sympathetic nervous system and HPA axis pathways. The catecholamines acting on alpha- and beta-adrenergic receptors increase cytokine expression in the brain and periphery. Further, catecholamines produce complex effects on immune cell subtypes and possess anti-inflammatory activity. On the other hand, regarding the HPA axis, cortisol is a very potent anti-inflammatory hormone, yet in chronic stress or depression, the immune system can become resistant to glucocorticoid. Antidepressant such as fluoxetine (selective serotonin reuptake inhibitor) has been shown to possess suppressive effects on the inflammatory response and on periodontal tissues in animal and the patients with periodontitis with clinical depression.

Depression may have an important bearing on plaque and periodontal disease, but this is important that the use of antidepressants must not degrade the periodontal condition. Various studies in the past have also stated a correlation between serum cortisol and severity of periodontitis. In this study, the cortisol level in patients on antidepressants and nonusers of cortisol was also estimated. We found that there was a minimal difference in cortisol levels in users of antidepressants as compared to nonusers, and the results were statistically not significant between the control group (Group I) and the study Groups II and III. The results of our study, therefore, signify that cortisol level is not associated with periodontal inflammation in depressed patients. Similarly, some animal studies have also demonstrated that certain antidepressants reduce the oxidative stress markers and decrease the severity of periodontal disease.

Although fluoxetine and venlafaxine both have been shown to inhibit the inflammatory response and the immune-modulating effects, their effect on chronic periodontitis appears not to be the same. The present study shows the comparison of the effects of these drugs on the basis of clinical parameters such as DI, CI, GI, periodontal PD (PPD), and clinical attachment level (CAL) in each study group. This study reveals that all of these clinical parameters were significantly different when compared in Groups I and II except DI which was not significant ($P = 0.3780$) in Groups 1 and III. However, they were not significantly different when compared with Group II.
### Table 2: Comparison of periodontal indices in the control group and the study Group II (fluoxetine)

| Study group | Group I (n=59) | Group II (n=62) | P       |
|-------------|----------------|----------------|---------|
| DI          | 1.37±0.68      | 1.74±0.56      | 0.3780* |
| CI          | 0.93±0.64      | 1.62±0.53      | 0.0001* |
| GI          | 0.96±0.70      | 1.49±0.51      | 0.0001* |
| PPD         | 2.69±0.72      | 3.15±0.84      | 0.0016* |
| CAL         | 3.14±0.85      | 4.31±1.25      | 0.0001* |

*P≤0.05 – Statistically significant. DI – Debris index; CI – Calculus index; GI – Gingival index; PPD – Probing probing depth; CAL – Clinical attachment loss; n – Number; P – P value

### Table 3: Comparison of periodontal indices in the control group and the study group III (venlafaxine)

| Study group | Group I (n=59) | Group III (n=61) | P       |
|-------------|----------------|-----------------|---------|
| DI          | 1.37±0.68      | 1.67±0.51       | 0.0071* |
| CI          | 0.93±0.64      | 1.72±0.71       | 0.0001* |
| GI          | 0.96±0.70      | 1.42±0.51       | 0.0001* |
| PPD         | 2.69±0.72      | 3.4±0.42        | 0.0001* |
| CAL         | 3.14±0.85      | 4.20±0.34       | 0.0001* |

*P≤0.05 – Statistically significant. DI – Debris index; CI – Calculus index; GI – Gingival index; PPD – Probing probing depth; CAL – Clinical attachment loss; n – Number; P – P value

and III. This indicates that antidepressants significantly altered periodontal health. Although they have been shown to possess anti-inflammatory properties, they did not contribute in reverting the periodontal inflammation. The DI which was not significantly affected in Group I and Group II presents ineffectiveness of the therapy. Our results are in accordance with the findings of Carvalho et al.[20] They concluded from their study on animal model that tissue damage in their study was associated with bone loss, inflammatory response, and increased immune reactivity.

This study shows that the clinical periodontal parameters DI, CI, GI, PPD, and CAL were significantly higher in patients receiving fluoxetine (Group II) compared with control (Group I) [Tables 2 and 3, Figure 1]. This indicates that the depressed patients taking fluoxetine are not protected against the periodontal inflammation. Our findings are in contrast to the findings of Eren et al.[21] who found that GI, PPD, and attachment level were lower in patients receiving fluoxetine and suggest that regular professional oral health care should be rendered to every depressed patient receiving such therapy.

Thus, the claim that fluoxetine inhibits inflammatory response, periodontal severity, and bone loss[21] could not be proved in this study. Thus, on the basis of observations, it can be established that the anti-inflammatory effects of fluoxetine are nullified at periodontium level, which may be possible due to regular effects of toxins and enzymes released by plaque micro-organisms.

**CONCLUSION**

The patients on antidepressants such as venlafaxine or fluoxetine protect the periodontium due to their anti-inflammatory properties, but these drugs may be considered as a risk factor of periodontal disease. Although it is not necessary for the treating dentist to diagnose a depressive condition, familiarity with the patient’s medical history, current prescriptions, and general indicators of depression could alert the dentist for possible problems and facilitate an appropriate referral for evaluation of the depressive symptoms.

Further studies are required to confirm the role of antidepressants as a risk factor for periodontal disease focusing on drug intake over the specified time period and also on the role of individual drugs.

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**Conflicts of interest**
There are no conflicts of interest.

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