Reduction of Pain and Depression in Occlusal Splint-Based Treatment for TMD is Accompanied with Increase in Urinary Serotonin

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Abstract: The aim of this study was to assess the parallel effects of an occlusal splint-based intervention for TMD on urinary serotonin levels, depression and pain. Previous RCT studies have shown that occlusal splint-based treatment reduce pain and depression, but have not measured serotonin. 15 patients (four males and 11 females) completed an intervention protocol with a silicone dental splint for 60 days. Patients were assessed before and after treatment for urinary serotonin levels, TMD-related pain and depression symptoms (self-reports). Results showed a significant increase in urinary serotonin levels between the two assessments along with a reduction in pain and depression. Overall results suggest that the positive effects of occlusal-based treatment on physical and mental health could be related to increases in serotonin levels.

Keywords: TMD, Occlusal splint, Urinary Serotonin, Depression, Pain.

INTRODUCTION

Temporomandibular joint dysfunctions or disorders (TMDs) of the stomatogmathic system are a type of prevalent and disabling condition that may involve not only physical, but also psychological outcomes. Depression, in particular, is particularly common among TMD patients [1], resulting from the chronic pain usually associated with TMD [2]. Depression is one of the most prevalent mental health conditions in developed world [3], and neurobiological evidence suggests that it is associated to failure of the trimonoaminergic neurotransmitter system, particularly in the serotoninergic pathways [for a review, see 4]. In other words, serotonin levels are usually negatively correlated with depression.

Pain symptoms related to TMDs can be treated with occlusal appliances or splints, which are dental splints specially devised for masticatory muscle relaxation and protection of teeth from grinding movements. A recent meta-analysis of randomized controlled trials (RCTs) of occlusal splints concluded that well-adjusted, hard occlusal stabilization appliances designed to promote relaxation have a significantly higher efficacy in the treatment of TMD pain when compared to non-occluding appliances and no treatment [5]. A more recent study similarly found that occlusal splints accelerated the effects of behavioral change-based therapy in reducing TMD-related pain [6]. Furthermore, at least one RCT study found that the effects of occlusal splint on reducing TMD carry over to reduction of depression symptoms [7].

In short, previous studies have found that treatments of TMD with occlusal splints have effects on both pain symptoms and depression, and we also know that depression is associated to lower levels of serotonin. What is not yet known is whether the effects of occlusal splints on reduction of pain symptoms and depression are also associated with predictable increases in serotonin levels. Evidence in favor of this association would provide further support for the effect of this sort of treatment on the reduction of depression, which is important because this is a low-cost type of treatment and may help reduce at the same time general and mental health care costs. The current study thus assessed the association of TMD pain symptoms, depression and serotonin urinary levels in the context of a TMD intervention with intraoral application of occlusal splints.

TMD, Pain, Depression, and Serotonin

TMDs are disorders that affect 3% to 15% of the population in Western societies [8]. In some regions, symptoms suggestive of TMD have been detected in up to 50% of the general population [9, 10] TMD refers to a broad set of stomatognathic conditions that affect mainly the temporomandibular joint (TMJ) and the mastigatory muscles [11]. TMDs have been classified as musculoskeletal disorders; their most common clinical signs are TMJ sounds and impaired mandibular

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activity [12], as well as dramatic pain, which is typically located in the masticatory muscles and the preauricular area [13], but can also manifest itself as migraine headache [14]. The predisposing factors of TMD include systemic, structural and psychological [15]. Parafunctional habits are the main cause of disturbances that enhance the progression of temporomandibular dysfunction, but psychological changes, such as depressive mood states and stress, can also predispose to or sustain TMD [for a review 16].

Conversely, TMD also sustains depression, anxiety and somatization, which are common psychiatric disorders among TMD patients; of these, depression is the most frequent (1). The available evidence points to pain as the main mediator of the effect of TMD on depression [17]. Previous studies have indicated that patients with pain caused by TMD are more likely to display affective disorders such as depression or anxiety [2]. Neuroimaging evidence also suggests that the patterns of neural activity are modified with the pain and suffering [18]: the painful stimulus activates the anterior cingulate gyrus cortex, the primary and secondary somatosensory cortex, insula, thalamus and prefrontal cortex. The change caused by TMD through pain may thus interfere with cognitive function, leading to cognitive dysfunction and emotional imbalance [19, 20].

Neurobiological research has also found that depression results from failures of the trimonoaminergic neurotransmitter systems, in particular in the serotoninergic pathways in mood or affective disorders [21]. The main serotoninergic pathways project their axons to the pre-frontal cortex, where higher-order cognitive functions and emotional processing occur. Disruption of these pathways and subsequent information processing deficits in prefrontal regions may trigger depressive symptomatology along with other psychiatric or cognitive disturbances [22, 23]. Serotonin is thus considered one of the main neurotransmitters involved in depression [4]. The action of serotonin (5-hydroxytryptamine, 5-HT) in the synapse is terminated by monoaminoxidase enzyme activity and neuronal uptake pump for 5-HT, which allows reuse of the 5-HT molecules in the presynaptic neuron. Regulatory mechanisms such as these are the main targets of first-line antidepressant agents, which boost the synaptic action of 5-HT [24].

Study Overview

Several treatment methods have been developed to relieve tension in TMD. Although combined treatments based on intraoral appliances and biofeedback procedures can produce more pain relief in TMD patients [see 5 for a review], most dental clinicians do not have the means or training to implement them. On the other hand, the use of occlusal splints to promote muscle relaxation of the TMJ is widespread, and there is evidence of its effectiveness at that level[5]. Previous studies have suggested that these methods are indeed effective in reducing depression [6]. However, evidence concerning the therapeutic effects of occlusal splint treatments on serotonergic pathways, the dysfunction of which is associated to depression, are still lacking. Thus, in this study we aimed to assess the effects of an intraoral treatment with application of occlusal splint at the same time on pain relief, depression symptoms, and urinary serotonin levels in TMD patients. We opted for a pre-and-post-treatment assessment, rather than a randomized control trial, for logistical limitations (i.e., the study was carried out in a private dental practice with free treatment as motivation for participation and it would have been extremely difficult to place participants in a waiting list control). However, as it is already well-established in the literature that treatment with occlusal splints reduces pain and depressive symptoms, we were simply interested in knowing whether, if we found a reduction in TMD pain and depression, there would also be a parallel effect on boosting of urinary serotonin levels, consistent with a positive effect of treatment. We were also interested in assessing the pattern of associations between TMD pain symptoms, depression, and serotonin levels both pre and post-treatment. Together with the predicted effects, positive correlations between pain and depression and negative correlations of both with serotonin levels at both pre and post treatment moments would be consistent with a positive effect of treatment at varying original levels of TMD.

MATERIALS AND METHODS

Patients

45 patients were recruited from two dentistry and otolaryngology practices in Lisbon, Portugal in exchange for free treatment with occlusal splints. Inclusion criteria were that patients (a) be diagnosed with TMD according to the Research Diagnostic Criteria for TMD - RDC/TMD [25]; (b) were not undergoing treatment in psychiatry, neurology or other medical specialty, in which they could not stop the medication; and (c) did not have stomatognathic conditions that might interfere with the silicon dental splint treatment. Patients identified as potential

participants attended a screening session consisting of a standardized clinical history assessment on the basis of the RDC/TMD criteria. Selected participants were instructed (a) to follow a strict diet plan without foods rich in tryptophan (e.g., cheese), which is a serotonin precursor, for at least two weeks before urinary collection, (b) to abstain from taking medicine such as antipsychotics, antidepressants, aspirins, anti-inflammatories, tetracycline, anxiolytics and monoamine oxidase inhibitors for that period, and (c) to abstain from smoking, taking coffee or drinking alcohol for at least 48 hours before urinary 5-HT assessments. 26 patients had to be excluded after post-treatment screening due to non-fulfillment of these recommendations, and an additional 4 due to poorly-fitting dentures. A final sample of 15 patients (mean age 41.0 ± 13.8 years, min age 21, max age 65; 4 male, 11 female; mean education 12 ± 2.8 years) underwent two complete evaluations. Four of the patients were smokers. During the pre-study screening, patients reported frequent suffering from headaches or pain in adjacent head regions: 13 reported pain in the TMJ, 3 also reported pain in the ear, and 11 in the neck; 12 patients had TMJ crepitus and tinnitus.

Materials

Physical symptoms and quality-of-life impact of TMD were measured with a standard measure of social impact of oral health: the short form of the Oral Health Impact Profile - OHIP-14 [26] derived from the original version with 49 items [27]. 14 items measure (α = .88) frequency of negative impacts (e.g. “Have you had painful aching in your mouth?”; “Have you had to interrupt meals because of problems with your teeth or mouth?”) on 5-point scales (Always = 4; Frequently = 3; Sometimes = 2; Rarely = 1; or Does not apply = 0). The total score is computed by averaging all the responses. Scores between (0 – 1) indicate the absence of TMD; scores between (1 - 2) suggest mild to moderate TMD; between (2 - 3) moderate to severe TMD, whereas average scores between (3 - 4) suggest acute TMD condition.

Depression was assessed with the Beck Depression Inventory – BDI [28]. Recommended cut-off scores are: with no depression or mild depression (0 to 10); mild to moderate depression (10 to 18); moderate to severe depression (19 to 29); and severe depression (30 to 63). This scale is organized into 21 items that are assessed on a 4-point scale (e.g. from “I do not feel sad” to “I am so sad or unhappy that I can't stand it”). The original version of the BDI [28] showed good internal consistency (α = .86).

Urinary serotonin concentration: sample collections were performed in 24-hour urine. 5-HT levels in urinary samples were estimated with high performance liquid chromatography (HPLC) with the reagent kit for the HPLC analysis of serotonin in urine (Chromsystems®).

Procedure

In each of the two dental clinics involved, dental clinicians identified patients with visible probable signs of TMD, such as misalignment of teeth or lack of vertical dimension of dentition. In both types of cases there is a bad relation of the mandibular condyle to the glenoid cavity – which has a destructive impact on the ligaments of the articular disc and the glenoid. They palpated those patients with a light pressure on the TMJ in order to check for confirmatory signs such as crepitation or subluxation of the TMJ. Upon identification of these TMJ signs, the clinician interrogated the patients on TMJ symptoms in order to confirm the preliminary diagnostic. Finally, radiographic exams were carried out to observe discrepancies in the linear and angular measures of the dental system.

Patients who were diagnosed as suffering from TMD were then invited to participate in a study on the effects of occlusal splint-based treatment in exchange for free treatment. Treatment began immediately after they had given their written informed consent to treatment and assessments. The dental clinician made plaster casts of the patients’ dentures from alginate or elastomer molds taken directly from patients mouths, and then used the plaster casts to produce the occlusal splints from silicone plates of personalized thickness in *Dentalflux Pr* vacuum devices.

The pre-treatment assessment consisted of the OHIP-14 and the BDI for depression assessment. Urinary samples were collected one day before evaluation and were stored at 5ºC up to 24 hours. Participants were then subjected to an intervention protocol with a silicone splint modeled to their dentures for at least 12 hours/day during a 60-days period. The post-treatment assessment was performed with the same evaluation procedures as the pre-treatment assessment.

RESULTS

Repeated-measures ANOVAs (before vs. after intervention) were used to compare TMD outcomes,

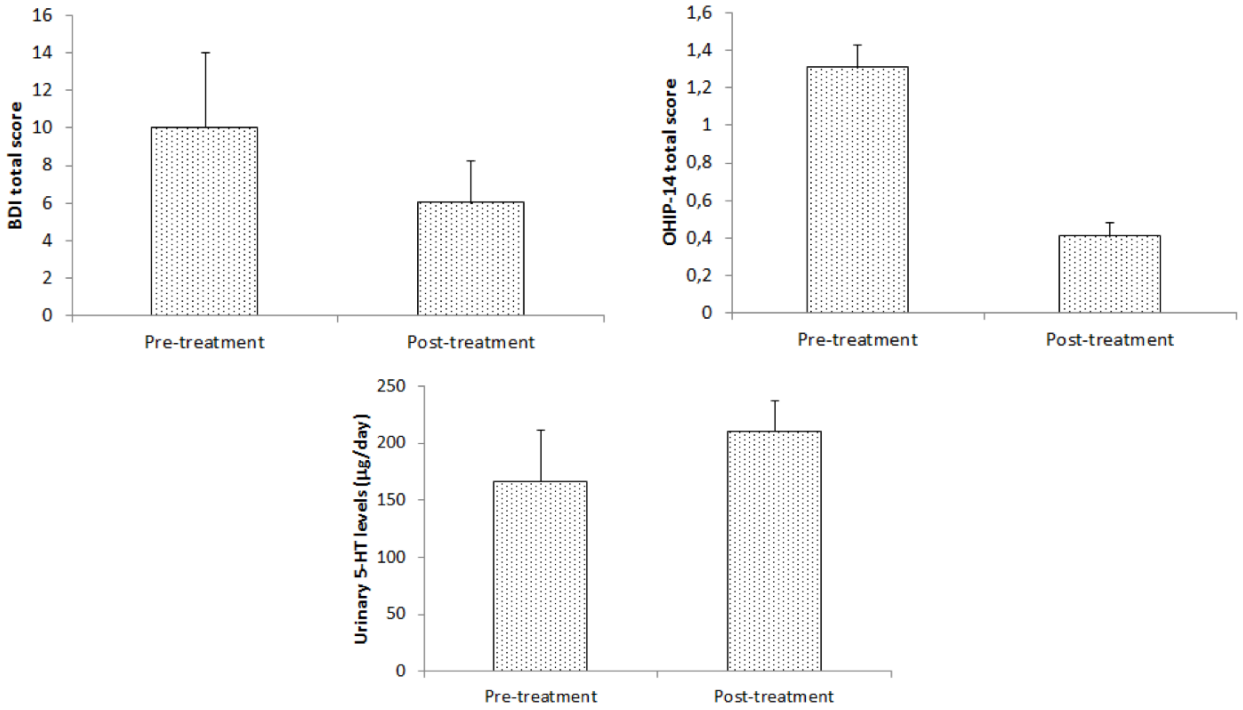

Figure 1: Differences between pre- and post treatment assessments for depression, physical symptoms and urinary 5-HT levels.

depression, and urinary serotonin levels in the pre- and post-treatment assessments (Figure **1**). We also report the correlations between these three variables in each of these moments.

Pre-treatment, serotonin correlated negatively and moderately (though not significantly) with both other variables (with TMD symptoms r = -.44; with depression = -.45). However, the two subjective outcomes of depression and TMD were strongly and significantly correlated at pre-treatment (r = .67).

The results revealed a significant decrease in TMD (OHIP-14) outcomes, F (1, 14) = 28.132, p<.001, η^2 = 0.51, from 1.30 (SD = 0.25) in the pre-treatment to 0.41 (SD = 0.14) in the post-treatment assessment, which suggests an effect of improvement in physical outcomes of TMD resulting from the intervention with the silicon dental splint.

We also found a decrease in depression between the two assessments (F (1, 14) = 14.692, p<.001; η^2 = .43, from pre-treatment (M = 9.60; SD = 7.98) to post-treatment (M = 5.80; SD = 5.44) (Figure **1**). According to the cut-off points from the original version of the BDI [28], the number of clinical depression cases decreased from the first assessment (3 cases of mild to moderate and 4 cases moderate to severe depression) to the second assessment (only 3 cases of mild to moderate depression, which had all been classified as having severe depression in the first assessment).

Finally, we also found an increase in serotonin levels. In order to compare the urinary 5-HT levels between the two assessments, a repeated measures ANOVA was also performed with one within-subjects factor (before vs. after intervention). The results indicated statistically significant differences between the two assessments (F(1, 14)= 10.054; p<.01; η^2 = .42). The urinary 5-HT levels were lower at pre-treatment (M = 165.92; SD = 23.45) than post-treatment (M = 210.11; SD = 13.70). These data reveal an increase in urinary 5-HT levels after intervention with the silicone dental splint (Figure **1**). The power of these three tests was higher than 80%.

We also found strong correlations between pre- and post-treatment levels of all three dependent variables: TMD, r = .43; depression, r = .74; and serotonin, r = .85. This indicates that the effect of the treatment found on all three variables operates independently of their initial level, and suggests that treatment could be beneficial even for patients with mild initial levels of TMD.

Finally, a similar pattern of correlations to that of pre-treatment was found at post-treatment: assessment for serotonin with TMD symptoms (r = -.27) and

depression (r = -.34), and between TMD symptoms and depression (r = .41); due to the small sample size, however, none of these effects was significant at $p < .05$.

DISCUSSION AND CONCLUSIONS

In this study, we assessed whether an intervention with a silicone dental splint (i.e., occlusal splint) would have parallel effects on subjective outcomes of TMD (depression and social and pain outcome) as well as on levels of urinary serotonin (5-HT). We expected that this intervention would relieve pain associated to muscular tension in the TMJ and therefore decrease psychiatric comorbidity, relieving depression and improving the level of peripheral 5-HT.

Our results show the expected increase in peripheral 5-HT levels, along with a reduction of clinical depression to subclinical depression scores with treatment. These results are also consistent with the idea that relaxation of pain (in this case associated with TMD) may enhance the efficiency of the regulation of the serotonergic pathways to the prefrontal cortex, which in turn improves self-reported depression levels [4].

It should be noted that, although higher excretion rates of urinary 5-HT suggest an increase in availability of 5-HT within the brain and thus a probable disinhibiting of 5-HT neurons, this relation is not yet extremely well-established. Recent studies suggest that a substantial part of the serotonin found in urine is produced in the kidneys [29]. Future studies for 5-HT changes following interventions in TMDs would require measurement of plasma 5-HT.

In any case, our results suggest that it is possible not only to reverse the physical and the mental health consequences of TMDs with a simple intervention with a silicone dental splint, but that this effect is parallel to an improvement in urinary serotonin levels. This adds welcome support to a very cost-effective way of improving widespread physical and mental health problems, and one which has not yet received the attention it deserves.

The fact that previous studies found positive effects of this sort of treatment on the reduction of pain and depression [5-7] indicates that this result was probably not due to the positive psychological effect of being in a treatment group, but rather reflects an actual effect of the treatment, despite the small size of our sample (due to a large exclusion rate) and the fact that we did not have a control group. Further studies are however needed to better test the direct effect of occlusal splint-based treatment on serotonin levels.

REFERENCES

[1] Manfredini D, Bandettini di Poggio A, Cantini E, Dell'Osso L, Bosco M. Mood and anxiety psychopathology and temporomandibular disorder: a spectrum approach. J Oral Rehabiliat 2004; 31: 933-40. http://dx.doi.org/10.1111/j.1365-2842.2004.01335.x

[2] Speculand B, Goss AN, Hughes A, Spence ND, Pilowsky I. Temporo-mandibular joint dysfunction: pain and illness behaviour. Pain 1983; 17(2): 139-50. http://dx.doi.org/10.1016/0304-3959(83)90138-0

[3] Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, *et al*. Cross-national epidemiology of DSM-IV major depressive episode. BMC Med 2011; 9: 90. http://dx.doi.org/10.1186/1741-7015-9-90

[4] Willner P, Scheel-Krüger J, Belzung C. The neurobiology of depression and antidepressant action 2012; pii: S0149-7634(12)00216-3. [Epub ahead of print].

[5] Fricton J, Look JO, Wright E, Alencar FG Jr, Chen H, Lang M, Ouyang W, Velly AM. Systematic review and meta-analysis of randomized controlled trials evaluating intraoral orthopedic appliances for temporomandibular disorders. J Orofacial Pain 2010; 24(3): 237-54.

[6] Conti PC, de Alencar EN, da Mota Corrêa AS, Lauris JR, Porporatti AL, Costa YM. Behavioural changes and occlusal splints are effective in the management of masticatory myofascial pain: a short-term evaluation. J Oral Rehabilit 2012; 39(10): 754-60. http://dx.doi.org/10.1111/j.1365-2842.2012.02327.x

[7] Turk DC, Zaki DS, Rudy TE. Effects of intraoral appliance and biofeedback/stress management alone and in combination in treating pain and depression in patients with temporomandibular disorders. J Prosthetic Dent 1993; 70: 158-64. http://dx.doi.org/10.1016/0022-3913(93)90012-D

[8] LeResche L. Epidemiology of temporomandibular disorders: Implications for the investigation of etiologic factors. Crit Rev Oral Biol Med 1997; 8: 291-305. http://dx.doi.org/10.1177/10454411970080030401

[9] Glass EG, McGlynn FD, Glaros AG, Melton K, Romans K. Prevalence of temporomandibular disorder symptoms in a major metropolitan area. Cranio 1993; 11(3): 217-20.

[10] Gesch D, Bernhardt O, Alte D, Schwahn C, Kocher T, John U, Hensel E. Prevalence of signs and symptoms of temporomandibular disorders in an urban and rural German population: Results of a population-based study of health in Pomerania. Quintessence Int 2004; 35: 143-50.

[11] De Leeuw R. Orofacial Pain: Guidelines for Assessment, Diagnoses and Management. Hanover Park, IL: Quintessence Publishing Co, Inc.; 2008.

[12] Ichesco E, Quintero A, Clauw DJ, Peltier S, Sundgren PM, Gerstner GE, Schmidt-Wilcke T. Altered functional connectivity between the insula and the cingulate cortex in patients with temporomandibular disorder: a pilot study. Headache 2012; 52(3): 441-54. http://dx.doi.org/10.1111/j.1526-4610.2011.01998.x

[13] Glaros AG, Glass EG. Temporomandibular disorders. In RJ Gatchel and EB Blanchard (Eds.), Psychophysiological disorders: Research and clinical applications (pp. 299-356). Washington, DC: American Psychological Association 1993. http://dx.doi.org/10.1037/10142-009

[14] Gonçalves DA, Bigal ME, Jales LC, Camparis CM, Speciali JG. Headache and symptoms of temporomandibular disorder: an epidemiological study. Headache 2010; 50(2): 231-41. http://dx.doi.org/10.1111/j.1526-4610.2009.01511.x

[15] Gameiro GH, Silva AA, Nouer DF, Ferraz MC. How may stressful experiences contribute to the development of temporomandibular disorders? Clin Oral Investig 2006; 10(4): 5-12. http://dx.doi.org/10.1007/s00784-006-0064-1

[16] Manfredini D, Landi N, Bandettini Di Poggio A, Dell'Osso L, Bosco M. A critical review on the importance of psychological factors in temporomandibular disorders. Minerva Stomatologica 2003; 52(6): 321-30.

[17] Manfredini D, di Poggio AB, Romagnoli M, Dell'Osso L, Bosco M. Mood spectrum in patients with different painful temporomandibular disorders. Cranio 2004; 22(3): 234-40. http://dx.doi.org/10.1179/crn.2004.028

[18] Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005; 9: 463-84. http://dx.doi.org/10.1016/j.ejpain.2004.11.001

[19] McCracken LM, Vowles KE. A prospective analysis of acceptance of pain and values-based action in patients with chronic pain. Health Psychol 2008; 27: 215-20.

[20] Eisenlohr-Moul TA, Burris JL, Evans DR. Pain Acceptance, Psychological Functioning, and Self-Regulatory Fatigue in Temporomandibular Disorder. Health Psychol 2012 [Epub ahead of print].

[21] Trachte GJ, Uncini T, Hinz M. Both stimulatory and inhibitory effects of dietary 5-hydroxytryptophan and tyrosine are found on urinary excretion of serotonin and dopamine in a large human population. Neuropsychiatric Disease Treatment 2009; 5: 227-35. http://dx.doi.org/10.2147/NDT.S5040

[22] Drevets WC, Gadde K, Krishnan R, in Neurobiology of Mental Illness, DS Charney, EJ Nester and BS Bunney, Eds. (pp. 394-418). Oxford Univ. Press, New York 1999.

[23] Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nat Med 2001; 7: 541-47. http://dx.doi.org/10.1038/87865

[24] Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. Sci STKE 2004; 16: (225).

[25] Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandibular Disord 1992; 6: 301-55.

[26] Slade GD. Derivation and validation of a short-form oral health impact profile. Commun Dent Oral Epidemiol 1997; 25(4): 284-90. http://dx.doi.org/10.1111/j.1600-0528.1997.tb00941.x

[27] Slade GD, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. Commun Dent Health 1994; 11(1): 3-11.

[28] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuringdepression. Archiv General Psychiatry 1961; 4: 561-71. http://dx.doi.org/10.1001/archpsyc.1961.01710120031004

[29] Wa TC, Burns NJ, Williams BC, Freestone S, Lee MR. Blood and urine 5-hydroxytryptophan and 5-hydroxytryptamine levels after administration of two 5-hydroxytryptamine precursors in normal man. Br J Clin Pharmacol 1995; 39(3): 327-9. http://dx.doi.org/10.1111/j.1365-2125.1995.tb04456.x

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