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ANXIOLYTIC ACTION OF DIAZEPAM AND ZOLPIDEM IN PATIENTS UNDERGOING EXTRACTION

Type of manuscript: Original study
Running title: Comparison of diazepam and zolpidem in patients undergoing extraction.

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Abstract:
Anxiolytic drugs are a class of drugs that reduce the anxiety levels in the individuals by nonspecifically binding to the GABAα located throughout the central nervous system. The aim of this study was to compare the anxiolytic effects of diazepam and Zolpidem in patients undergoing extraction. This was a cross sectional study conducted at a university setting, with a sample size of 100 patients, of the age group 25-45 years. 50 patients were administered with Tab. Diazepam and 50 patients with Tab. Zolpidem one hour before the surgical procedure. The Hamilton Anxiety Rating Scale (HAM A Scale) was used to record the patient's anxiety levels before and during the extraction procedure. These data were then recorded in MS Excel Sheet and imported to SPSS for statistical analysis. From this study, it can be seen that most of the patients were females and mainly between the age group 25-35 years. Therefore, it can be concluded that diazepam had better post sedation effects than zolpidem in patients undergoing extraction as patients presented with lesser severity in their anxiety levels. Diazepam had significantly lesser post sedation anxiety levels in comparison with its post sedation levels than zolpidem with $p<0.001$, statistically significant.
Keywords: Anxiety, Diazepam, Zolpidem

I. INTRODUCTION

Sedatives have been known for its efficacy for managing anxiety during dental treatment. Patients generally present with a moderate to high level of fear and anxiety during a surgical procedure (Domoto et al., 1991; Gatchel et al., 1983). Oral sedation helps the patients to combat mild to moderate levels of fear and anxiety, but they are commonly less effective in patients with higher levels of anxiety, and for these patients drugs can be administered intravenously for better action. On

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intravenous sedation, few individuals with higher levels of anxiety require a deeper level of sedation or general anaesthesia. The patient's age is an important factor in the selection of an oral sedative drug and it's dosage. The widely accepted is the oral route of administration as it is easy, painless, and inexpensive. Sedatives used to produce anxiolysis or minimal sedation in healthy adults are safe and effective at a required dosage (Malamed, 2006). For geriatric patients, it is important to select a particular dosage and drug as it may interact with the physiological and psychological changes, as older adults can have a higher risk of systemic diseases.

One of the commonly used sedatives are the benzodiazepines such as diazepam, zaleplon etc. They promote the binding to the inhibitory neurotransmitter, gamma aminobutyric acid (GABA) receptors in the brain. They are receptors of multi-subunit complexes associated with gated chloride ion (Cl−) channels that are seen within the cell membrane of neurons. When the receptor gets activated by GABA, the channel opens allowing greater influx of chloride ions and results in more negative resting membrane potential. This thereby results in sedation in individuals.

Zolpidem is also an anxiolytic non-benzodiazepine drug which binds to the omega 1 benzodiazepine recognition sites located within the GABAA receptor complex (Higashima et al., 1997). This is a highly lipophilic molecule and has fast onset of action (usually within 20–40 minutes), and peak plasma levels 1–2 hours after oral administration. Diazepam has 100% oral bioavailability and commonly used dosages are 2–10 mg for adults ("Inducible Transcription Factors in Neurons: The Missing Link in Adaptation? Tom Curran and James I. Morgan, Roche Institute of Molecular Biology, Nutley, NJ 07110," 1990). Zolpidem produces muscle relaxation and anticonvulsant effects in patients only at a higher dose than the hypnotic dose (Holm & Goa, 2000). Zolpidem has a rapid onset of action, usually within 30 minutes whereas it has a short half-life and no active metabolites. Flumazenil is the antagonist drug used for higher zolpidem sedation (Langtry & Benfield, 1990).

Extraction is one of the commonly performed surgical procedures in a dental clinic, and it is important to undergo a painless extraction in patients. Sedatives drugs play a major role in painless extractions as they block the neurotransmitters and suppress the anxiety levels and this will help in performing a successful procedure. Previously our department has published extensive research on various aspects of prosthetic dentistry (Anbu et al., 2019; Ariga et al., 2018; Ashok & Ganapathy, 2019; Duraisamy et al., 2019; "Evaluation of Corrosive Behavior of Four Nickel–chromium Alloys in Artificial Saliva by Cyclic Polarization Test:An in Vitro Study," 2017; Ganapathy et al., 2017; Gupta et al., 2018; Jain, 2017a, 2017b; Ranganathan et al., 2017; Varghese et al., 2019), this vast research experience has inspired us to research about comparison of anxiolytic drugs of diazepam and zolpidem in patients undergoing extraction.

II. MATERIALS AND METHODS

This was a cross sectional study conducted at a university setting, Chennai. The sample size was 100 patients, of the age group 25-45 years, with 50 males and 50 females. There were certain inclusion and exclusion criteria for sample selection. Inclusion Criteria included only patients undergoing extraction of root stumps and grossly decayed tooth. Exclusion Criteria was patients with systemic diseases and on medications, third molar impactions, mobile tooth, pregnant females, root canal treated tooth advised for extraction and in patients older than 45 years. Anxiolytic drugs such as Tab. Diazepam (10mg) and Tab. Zolpidem (10mg) were administered in patients undergoing extraction. 50 patients were administered

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with Tab. Diazepam and 50 patients were administered with Tab. Zolpidem one hour before undergoing the surgical procedure.

The Hamilton Anxiety Rating Scale (HAM A Scale) was used to record the patient's anxiety levels before and during the extraction procedure. This was distributed to patients undergoing extraction, before and after the drug was administered orally. This sheet had a series of scores from 0-4, and for each patient it was summed up to a total score of 56, in which a score of 17 or less indicates mild anxiety severity, 18 to 24 indicates mild to moderate anxiety severity, 25 to 30 indicates a moderate to severe anxiety severity.

These data were then recorded in MS Excel Sheet and imported to SPSS for statistical analysis. The statistical tests used were the inferential tests (chi square test) and the descriptive statistics. Software used was the SPSS by IBM. The independent variables were age and gender. The dependent variables were HAM A scale scores for Diazepam and Zolpidem, pre and post sedation. Graphical illustration was done using SPSS Version 20.0.

III. RESULTS AND DISCUSSION

In this study, it can be seen that 58.0% of the patients were distributed in the age group between 25-35 years and 42.0% of the patients were in the age group between 36-45years (Figure 1) and 51% of the study population were females and 49% of subjects were males (Figure 2). Based on pre sedation HAM A scores for diazepam, 68.9% of the patients had a score between 18-24, 18% had a score between 25-30 and 14% had a score of <17 (Figure 3). Based on post sedation HAM A scores of diazepam, 58% of the patients had a score between 18-24, 34% had a score of <17 and 8% had a score between 25-30 (Figure 4). Based on pre sedation HAM A scores for zolpidem, 56% of the patients had a score between 18-24, 24% had a score of <17 and 20% had a score between 25-30 (Figure 5). Based on post sedation HAM A scores for zolpidem, 54% of the patients had a score between 18-24, 42% had a score of <17 and 4% had a score between 25-30 (Figure 6). On association between age and HAM A scores of pre and post sedation with diazepam, in 25-35 years age group, a higher mean score of 1.76 was seen for pre sedation and there was decrease in the mean score (1.41) after post sedation with diazepam, whereas in 36-45 years age group, a higher mean score of 2.43 was seen for pre sedation and there was decrease in the mean score (2.19) after post sedation with diazepam, p value- 0.00 (<0.05), statistically significant (Figure 7). On association between age and HAM A scores of pre and post sedation with zolpidem, in 25-35 years age group, a higher mean score of 1.59 was seen for pre sedation and there was decrease in the mean score (1.28) after post sedation with zolpidem, whereas in 36-45 years age group, a higher mean score of 2.48 was seen for pre sedation and there was decrease in the mean score (2.10) after post sedation with zolpidem, p value- 0.01 (<0.05), statistically significant (Figure 8). On association between gender with pre and post sedation with diazepam, in females, a higher mean score of 1.73 was seen for pre sedation and there was decrease in the mean score (1.33) after post sedation with diazepam, whereas in males, a higher mean score of 2.37 was seen for pre sedation and there was decrease in the mean score (2.16) after post sedation with diazepam, p value- 0.20 (>0.05), statistically insignificant (Figure 9). On association between gender with pre and post sedation with zolpidem, in females, a higher mean score of 1.53 was seen for pre sedation and there was decrease in the mean score (1.18) after post sedation with zolpidem, whereas in males, a higher mean score of 2.41 was seen for pre sedation and there was decrease in the mean score (2.08) after post sedation with zolpidem, p value- 0.019 (<0.05), statistically significant (Figure 10).

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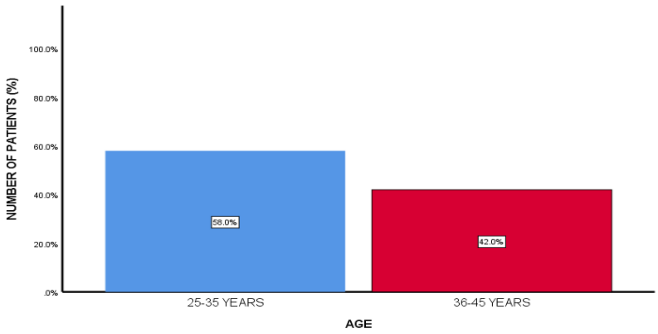

Figure 1: Bar graph represents the distribution of patients based on age, where X-axis represents the age group of the patients and Y-axis represents the number of patients in percentage. 58.0% of the patients were distributed in the age group between 25-35 years (blue) and 42.0% of the patients were in the age group between 36-45years (red).

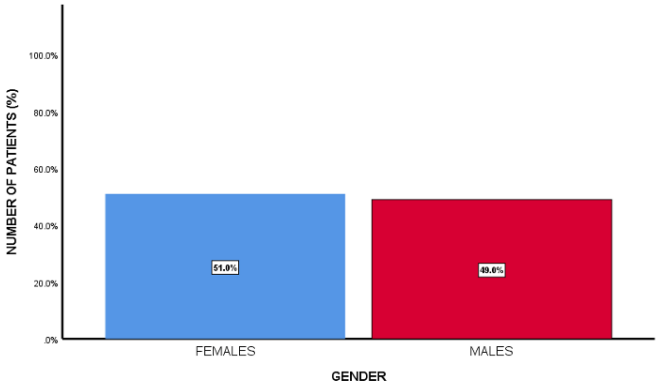

Figure 2: Bar graph represents the distribution of patients based on gender, where X-axis represents gender of the patients and Y-axis represents the number of patients in percentage. 51% of the study population were females (blue) and 49% of subjects were males (red).

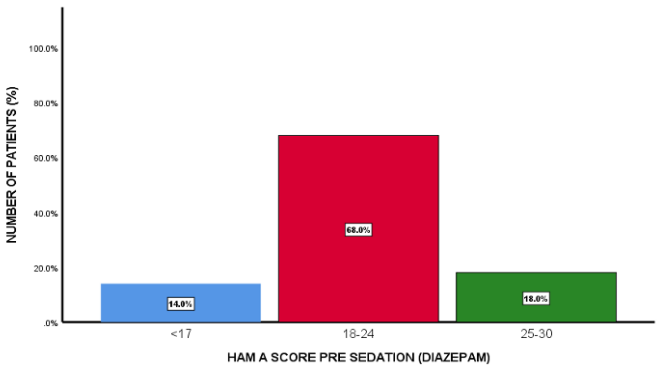

Figure 3: Bar graph represents the distribution of patients based on Pre sedation HAM A scores in patients administered with Diazepam, where X-axis represents the pre sedation HAM A scores for Diazepam) and Y-axis represents the number of patients in percentage. 68.9% of the patients had a score between 18-24 (red), 18% had a score between 25-30 (green) and 14% had a score of <17 (blue).

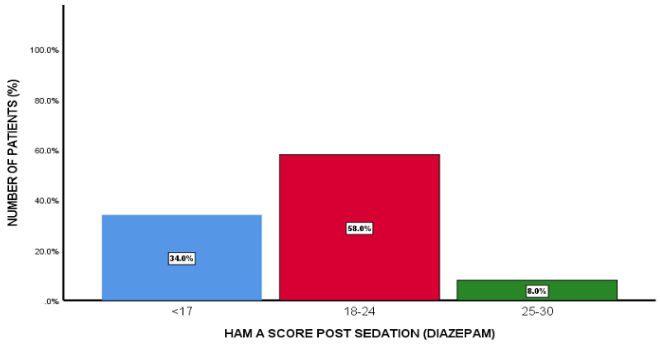

Figure 4: Bar graph represents the distribution of patients based on Post sedation HAM A scores in patients administered with Diazepam, where X-axis represents the post sedation HAM A scores for Diazepam) and Y-axis represents the number of patients in percentage. 58% of the patients had a score between 18-24 (red), 34% had a score of <17 (blue) and 8% had a score between 25-30 (green).

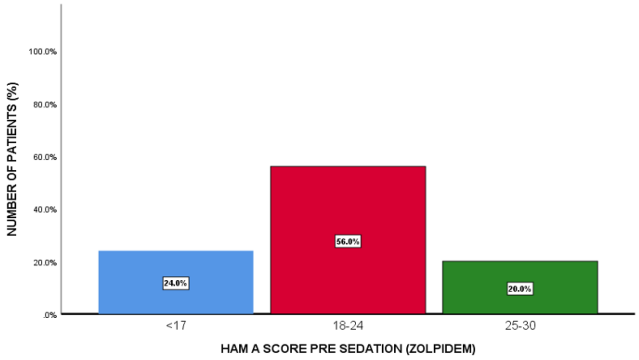

Figure 5: Bar graph represents the distribution of patients based on Pre sedation HAM A scores in patients administered with Zolpidem, where X-axis represents the pre sedation HAM A scores for Zolpidem) and Y-axis represents the number of patients in percentage. 56% of the patients had a

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score between 18-24 (red), 24% had a score of <17 (blue) and 20% had a score between 25-30 (green).

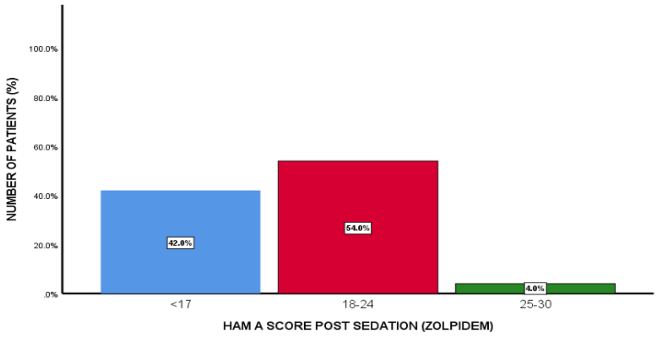

Figure 6: Bar graph represents the distribution of patients based on Post sedation HAM A scores in patients administered with Zolpidem, where X-axis represents the post sedation HAM A scores for Zolpidem) and Y-axis represents the number of patients in percentage. 54% of the patients had a score between 18-24 (red), 42% had a score of <17 (blue) and 4% had a score between 25-30 (green).

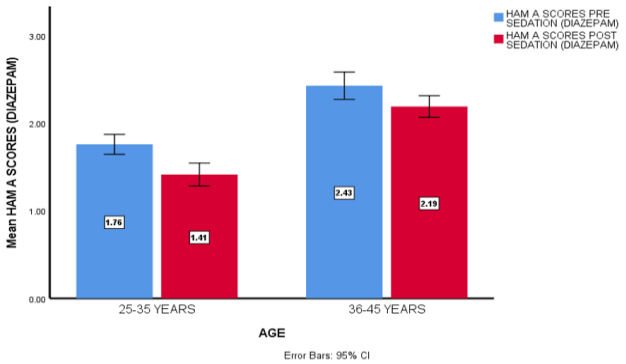

Figure 7: Bar graph represents the association between age with Pre and post sedation HAM A scores in patients administered with Diazepam where X-axis represents the age of the patients and Y-axis represents the Mean HAM A scores for Diazepam. In 25-35 years age group, a higher mean score of 1.76 was seen for pre sedation and there was decrease in the mean score (1.41) after post sedation with diazepam, whereas in 36-45 years age group, a higher mean score of 2.43 was seen for pre sedation and there was decrease in the mean score (2.19) after post sedation with diazepam.

[Pearson chi square test, chi square value- 18.34, p value- 0.00 (<0.05), statistically significant]

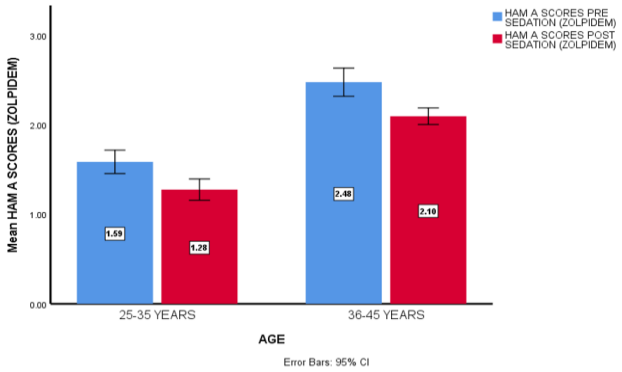

Figure 8: Bar graph represents the association between age with Pre and post sedation HAM A scores in patients administered with Zolpidem where X-axis represents the age of the patients and Y-axis represents the Mean HAM A scores for Zolpidem. In 25-35 years age group, a higher mean score of 1.59 was seen for pre sedation and there was decrease in the mean score (1.28) after post sedation with zolpidem, whereas in 36-45 years age group, a higher mean score of 2.48 was seen for pre sedation and there was decrease in the mean score (2.10) after post sedation with zolpidem.

[Pearson chi square test, chi square value- 12.78, p value- 0.01 (<0.05), statistically significant]

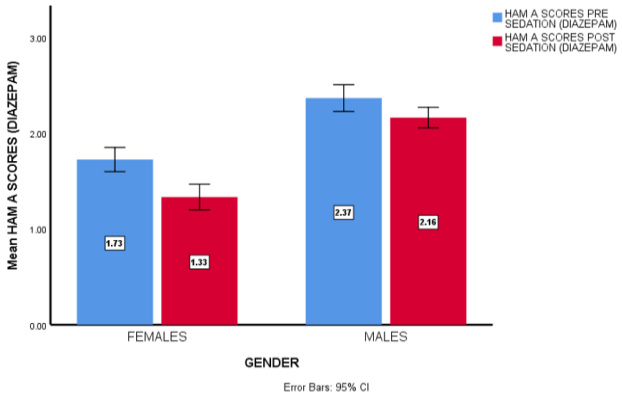

Figure 9: Bar graph represents the association between gender with Pre and post sedation HAM A scores in patients administered with Diazepam where X-axis represents the gender of the patients and Y-axis represents the Mean HAM A scores for Diazepam. In females, a higher mean score of 1.73

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was seen for pre sedation and there was decrease in the mean score (1.33) after post sedation with diazepam, whereas in males, a higher mean score of 2.37 was seen for pre sedation and there was decrease in the mean score (2.16) after post sedation with diazepam.

[Pearson chi square test, chi square value- 5.973, p value- 0.20 (>0.05), statistically insignificant].

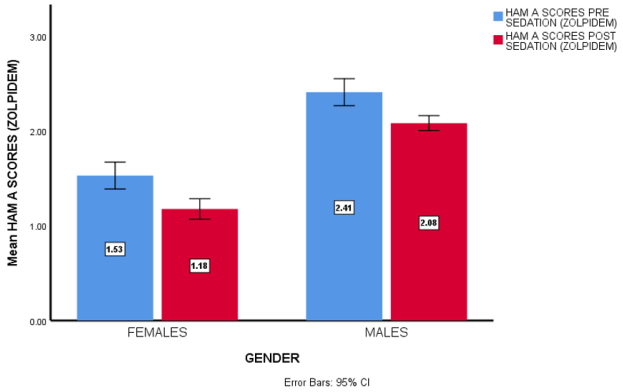

Figure 10: Bar graph represents the association between gender with Pre and post sedation HAM A scores in patients administered with Zolpidem where X-axis represents the gender of the patients and Y-axis represents the Mean HAM A scores for Zolpidem. In females, a higher mean score of 1.53 was seen for pre sedation and there was decrease in the mean score (1.18) after post sedation with zolpidem, whereas in males, a higher mean score of 2.41 was seen for pre sedation and there was decrease in the mean score (2.08) after post sedation with zolpidem.

[Pearson chi square test, chi square value- 21.82, p value- 0.019 (<0.05), statistically significant]

	PRE-SEDATION MEAN HAM-A SCORES	POST SEDATION MEAN HAM-A SCORES	P VALUE
DIAZEPAM (n=50)	4.1	3.49	0.20 (>0.05)
ZOLPIDEM (n=50)	3.94	3.26	0.019 (<0.05)

Table 1: Table representing the pre-sedation and post-sedation HAM-A scores for Diazepam and Zolpidem with their respective p-values.

There are a wide variety of drugs which can be used to sedate patients undergoing extraction (Monteserin-Matesanz et al., 2015). However, there are a few studies that relatively compare the effectiveness of different kinds of sedatives. Benzodiazepines are the class of drugs mostly used to induce a state of anxiolysis, sedation, or amnesia (Surendar et al., 2014). It can also be seen that a lesser dose of diazepam also produces better post sedation zolpidem, and hence can be used to prevent any adverse effects in the adults. Diazepam is known to attain the sedative level about 30 minutes after oral administration, and deepest sedative effects after 60-90 minutes (Breimer, 1977). Although diazepam and zolpidem is known to produce adverse effects such as nausea, vomiting and respiratory depression , our study revealed no such effects during and after the procedure (Yanase et al., 2009).

IV. CONCLUSION

Within the limitations of this study such as small sample size and geographic limitations, it can be concluded that diazepam had better post sedation effects than zolpidem in patients undergoing extraction. Diazepam had significantly lesser post sedation anxiety levels than zolpidem with p<0.001. However, further studies have to be done to evaluate the anxiolytic effects of these drugs in patients undergoing surgical procedures.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

V. REFERENCES

[1]. Anbu, R. T., Suresh, V., Gounder, R., & Kannan, A. (2019). Comparison of the Efficacy of Three Different Bone Regeneration Materials: An Animal Study. *European Journal of Dentistry*, *13*(1), 22–28.

[2]. Ariga, P., Nallaswamy, D., Jain, A. R., & Ganapathy, D. M. (2018). Determination of Correlation of Width of Maxillary Anterior Teeth using Extraoral and Intraoral Factors in Indian Population: A Systematic Review. *World Journal of Dentistry*, *9*(1), 68–75.

[3]. Ashok, V., & Ganapathy, D. (2019). A geometrical method to classify face forms. *Journal of Oral Biology and Craniofacial Research*, *9*(3), 232–235.

[4]. Breimer, D. D. (1977). Clinical pharmacokinetics of hypnotics. *Clinical Pharmacokinetics*, *2*(2), 93–109.

[5]. Domoto, P., Weinstein, P., Kamo, Y., Wohlers, K., Fiset, L., & Tanaka, A. (1991). Dental fear of Japanese residents in the United States. *Anesthesia Progress*, *38*(3), 90–95.

[6]. Duraisamy, R., Krishnan, C. S., Ramasubramanian, H., Sampathkumar, J., Mariappan, S., & Navarasampatti Sivaprakasam, A. (2019). Compatibility of Nonoriginal Abutments With Implants: Evaluation of Microgap at the Implant-Abutment Interface, With Original and Nonoriginal Abutments. *Implant Dentistry*, *28*(3), 289–295.

[7]. Evaluation of Corrosive Behavior of Four Nickel–chromium Alloys in Artificial Saliva by Cyclic Polarization Test:An in vitro Study. (2017). *World Journal of Dentistry*, *8*(6), 477–482.

[8]. Ganapathy, D. M., Kannan, A., & Venugopalan, S. (2017). Effect of Coated Surfaces influencing Screw Loosening in Implants: A Systematic Review and Meta-analysis. *World Journal of Dentistry*, *8*(6), 496–502.

[9]. Gatchel, R. J., Ingersoll, B. D., Bowman, L., Cecilia Robertson, M., & Walker, C. (1983). The Prevalence of Dental Fear and Avoidance: A Recent Survey Study. In *The Journal of the American Dental Association* (Vol. 107, Issue 4, pp. 609–610). https://doi.org/10.14219/jada.archive.1983.0285

[10]. Gupta, P., Ariga, P., & Deogade, S. C. (2018). Effect of Monopoly-coating Agent on the Surface Roughness of a Tissue Conditioner Subjected to Cleansing and Disinfection: A Contact Profilometric Study. *Contemporary Clinical Dentistry*, *9*(Suppl 1), S122–S126.

[11]. Higashima, M., Kinoshita, H., Yamaguchi, N., & Koshino, Y. (1997). Differences in enhancing effects of zolpidem and benzodiazepine drugs on recurrent inhibition in rat hippocampal slices. In *Psychopharmacology* (Vol. 131, Issue 4, pp. 394–398). https://doi.org/10.1007/s002130050308

[12]. Holm, K. J., & Goa, K. L. (2000). Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs*, *59*(4), 865–889.

[13]. Inducible transcription factors in neurons:

Published by: The Mattingley Publishing Co., Inc.

November-December 2019
ISSN: 0193-4120 Page No. 6643 - 6650

The missing link in adaptation? Tom Curran and James I. Morgan, Roche Institute of Molecular Biology, Nutley, NJ 07110. (1990). In *Neurochemistry International* (Vol. 16, p. 2). https://doi.org/10.1016/0197-0186(90)90165-p

[14]. Jain, A. R. (2017a). Clinical and Functional Outcomes of Implant Prostheses in Fibula Free Flaps. *World Journal of Dentistry*, *8*(3), 171–176.

[15]. Jain, A. R. (2017b). Prevalence of Partial Edentulousness and Treatment needs in Rural Population of South India. *World Journal of Dentistry*, *8*(3), 213–217.

[16]. Langtry, H. D., & Benfield, P. (1990). Zolpidem. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. *Drugs*, *40*(2), 291–313.

[17]. Malamed, S. F. (2006). Sedation and safety: 36 years of perspective. *The Alpha Omegan*, *99*(2), 70–74.

[18]. Monteserin-Matesanz, M., Esparza-Gomez, G. C., Garcia-Chias, B., Gasco-Garcia, C., & Cerero-Lapiedra, R. (2015). Descriptive study of the patients treated at the clinic integrated dentistry for patients with special needs at Complutense University of Madrid (2003-2012). In *Medicina Oral Patología Oral y Cirugia Bucal* (pp. e211–e217). https://doi.org/10.4317/medoral.20030

[19]. Ranganathan, H., Ganapathy, D. M., & Jain, A. R. (2017). Cervical and Incisal Marginal Discrepancy in Ceramic Laminate Veneering Materials: A SEM Analysis. *Contemporary Clinical Dentistry*, *8*(2), 272–278.

[20]. Surendar, M. N., Natarajan Surendar, M., Kumar Pandey, R., Kumar Saksena, A., Kumar, R., & Chandra, G. (2014). A Comparative evaluation of Intrnasal Dexmedetomidine, Midazolam and Ketamine for their sedative and analgesic properties: A Triple Blind Randomized Study. In *Journal of Clinical Pediatric Dentistry* (Vol. 38, Issue 3, pp. 255–261). https://doi.org/10.17796/jcpd.38.3.l828585807482966

[21]. Varghese, S. S., Ramesh, A., & Veeraiyan, D. N. (2019). Blended Module-Based Teaching in Biostatistics and Research Methodology: A Retrospective Study with Postgraduate Dental Students. *Journal of Dental Education*, *83*(4), 445–450.

[22]. Yanase, H., Braham, R. L., Fukuta, O., & Kurosu, K. (2009). A study of the sedative effect of home-administered oral diazepam for the dental treatment of children. In *International Journal of Paediatric Dentistry* (Vol. 6, Issue 1, pp. 13–17). https://doi.org/10.1111/j.1365-263x.1996.tb00202.x