Antidepressants in Oral Health

Aman Sodhi*, Asha V*, Rajul Mehta**

*The Oxford Dental College , Banglore; **Ahemdabad Dental College And Hospital, Ahmedabad

Abstract : Orofacial pain has been one of the most perplexing conditions afflicting mankind. In an attempt to overcome pain, various drugs have been tried with success and limitations. Antidepressants have appreciable analgesic effect for the treatment of chronic orofacial pain. A sound knowledge of its effectiveness and safety is mandatory for the oral physicians. This article reviews the therapeutic and adverse effects of antidepressants. [Sodhi A et al NJIRM 2013; 4(3) : 149-153]

Key Words: Antidepressants, chronic orofacial pain, therapeutic uses, adverse effects

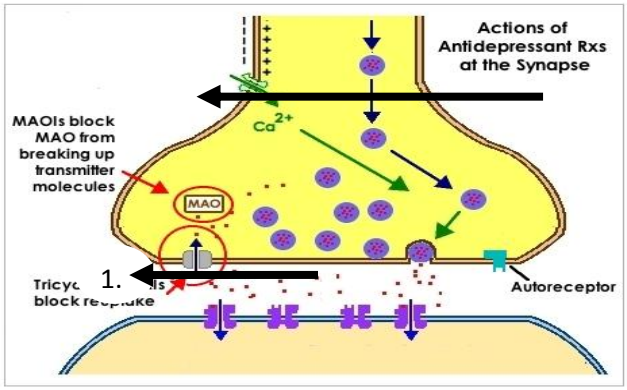
Author for correspondence: Dr. Aman Sodhi, The Oxford Dental College , Banglore.
e-mail: drrajul.mehta45@gmail.com

Introduction: Antidepressants are group of drugs used to prevent or treat depression. It is generally accepted that a relationship exists between chronic pain and depression. Several studies have demonstrated the analgesic efficacy of antidepressants in the treatment of chronic pain. The analgesic activity of this class of drugs is independent of its antidepressant effects and is attained at much lower doses. Amongst a wide variety of drugs coming under the umbrella of antidepressants, Tricyclic antidepressants (TCA) are of prime interest to the oral physicians. Selective agents might be safer and more effective

Table 1 : Classification: (based on mechanism of action) [1]

Selective serotonin reuptake inhibitors(SSRI)	Fluoxetine, Paroxetine,Sertraline, Fluvoxamine Citalopram, Escitalopram
Norepinephrine inhibitors	Desipramine, Nortriptyline,Maprotiline
Serotonin/norepinephrine reuptake inhibitors(SNRI)	***Tricyclics***– Amitryptiline,Doxepin,Clomipramine,Imipramine ***Non tryclics***-Duloxetine, Venlafaxine
Dopamine/norepinephrine reuptake inhibitors	Bupropion
Agents with atypical mixed actions	Mirtazapine, Nefazodone,Trazodone
MAO Inhibitors	Phenelzine, Tranycypromine, Isocarboxizid

Fig 1: Mechanism of analgesic action of antidepressants:



The TCAs and related drugs inhibit active reuptake of biogenic amines, noradrenaline (NA) and 5 hydroxytryptamine (5HT) into their respective neurons.[2] Thus enhance central inhibitory system in pain processing.

TCAs possess sodium, calcium and potassium channel blocking properties. [3] Sodium channel blocking properties of TCAs is robust. This will stabilize neurons, prevent peripheral sensitization and may underlie the mechanisms of peripheral analgesia. Regional application of TCA has an effect comparable to that of Local anesthetics[4]. The enhancement of inhibitory GABA and opiod effects are also present peripherally, increasing the analgesic effects of TCAs.[5] TCAs have moderate anti inflammatory action that would augment analgesia [6].

Indications in Oral Medicine: As adjuvant drug for management of chronic orofacial pain

- Trigeminal neuralgia
- Burning mouth syndrome
- Atypical facial pain
- Tension headache

- Migraine
- Post herpetic neuralgia
- Neurogenic pain unresponsive to narcotic analgesics
- Uncontrolled cancer pain
- Diabetic neuropathy
- Temporomandibular joint disorders
- Fibromyalgia
- Smoking cessation

Chronic Orofacial pain: Chronic pain is recognized as a complex disorder that is influenced by biologic factors and a range of psychosocial factors including emotion and psychological distress. According to IASP chronic pain is described as "a persistent pain that is not amenable as a rule, to treatments based on specific remedies, or to the routine methods of pain control such as non narcotic analgesics".[7]

Amitryptiline is probably the most frequently employed TCA in chronic orofacial pain syndrome.[8, 9]

Long half life (10-26hrs) of amitryptiline allows for once daily schedule. Treatment starts with a low dose of **20-25 mg of amitriptyline** to be taken before bedtime.[10] The dose needs to be adjusted according to two factors: (1) **pain control** and (2) **adverse reactions**. The dose is titrated at a rate of 10 mg a week to a maximum of 75 mg/day.

It is important to remember that there is 1 - 3 week delay in achieving maximum analgesic effect at any given dose. Consequently dose changes should not be made too rapidly unless adverse effects are extreme[10]. Therapy should be continued for 3 to 6 months before being slowly tapered and discontinued. Imipramine and Nortriptyline can be tried if amitryptiline is not effective.

Atypical Facial pain/atypical odontalgia/phantom pain: Atypical odontalgia according to International Headache society is defined as "Persistent facial pain that does not have the characteristic of the cranial neuralgia and is not attributed to any other disorder". It has been proposed that psychopathological factors are more significant hence Tricyclic antidepressants can be of help.[11] Venlafaxine 75 mg is effective in the treatment of atypical facial pain, the dose of which can be titrated to a maximum of 150 mg -225 mg/day after several weeks.[12]

Temporomandibular disorder (TMD): TMD is characterized by a combination of symptoms affecting the temporomandibular joint and/or masticatory muscles**.** The two most common clinical TMD symptoms are pain and dysfunction. Recent investigations into TMD have led to the recommendation of antidepressants as a supporting treatment against constant pain.

A double-blind study was conducted to verify the efficacy of antidepressants (amitriptyline) as a support in the treatment of chronic TMD pain wherein Group 1 was given 25 mg/day of amitriptyline and Group 2 with a placebo. The results revealed a significant reduction of pain and discomfort in Group 1 (75%) compared to Group 2 (28%).[13]

A study designed to evaluate long term effectiveness of low dose amitripyline (10-30 mg/day) in two groups of chronic TMD patients' revealed reduction in pain in both the groups.[14]

Chronic Tension Type Headache (CTTH): CTTH is characterized by bilateral tight band like discomfort that is present for greater than 15 days per month during a six month period.

***Amitriptyline*: (10-100mg/day)** can be considered efficacious in the prophylactic treatment of CTTH. Nevertheless, the combination of this treatment with other drugs or with behavioral therapies can provide a greater therapeutic efficacy[15].

Venlafaxine: Extended release has shown promising results in the prophylaxis of migraine and tension type headache Dose: 150-225 mg /day[16]

Trazdone hydrochloride, a nontricyclic antidepressant with strong sedating but with minimal anticholinergic effects and only mild to moderate cardiotoxocity can be given. Dosage: 50-100mg dose of trazdone hydrochloride to be taken at bed time to a max of 200-250 mg.

Post herpetic neuralgia (PHN): Herpes zoster of the maxillary and mandibular divisions is the cause of facial and oral pain. In majority of cases, the pain of herpes zoster resolves within a month after the lesions heal. Pain that persists longer than a month is classified as PHN, although some authors believe that pain should persist for longer than three or even six months.[17] PHN is often associated with significant morbidity and it can cause depression. The use of tricyclic antidepressants such as amitriptyline, nortriptyline, doxepin and desipramine is well established method of reducing the chronic burning pain that is characteristic of PHN.[18] A recent trial showed that desipramine is superior to amitriptyline for management of PHN.[19] Amitriptyline 10 mg – 100 mg /day: Nortriptyline 10-75 mg /day: Doxepin 10 -50 mg/day

Burning Mouth Syndrome: BMS is painful oral condition featuring burning sensations of the tongue, lips and mucosal regions of the mouth[20] A low dosage of tricyclic antidepressants may help reduce the pain associated with BMS .but it is usually avoided because of its anticholinergic effects (dry mouth). The tricyclic of choice is desipramin beginning with 25 mg at bedtime and escalating by 25 mg weekly upto 100mg/day or until symptoms resolve.[21]

Traumatic Neuropathy/ Traumatic Neuralgia

Amitriptyline: 25 to 50 mg per day may help reduce pain experienced with traumatic neuralgia but rarely completely resolves the condition [22]

Imipramine: widely used in the treatment of traumatic neuropathies and maybe tried when amitryptiline is not tolerated or is ineffective. Dosage: 12.5 mg daily (half tab) and slowly titrated upto 25-50 mg daily.[23]

Bupropion: It is effective in treatment of neuropathic pain. Dosage: 150 mg twice daily, results in pain relief by second week.[24]

Cancer pain: In cancer patients tricyclic antidepressants can be used as adjuvant medication which may enhance the analgesic effects of other agents, possess analgesic potential themselves, and promote sleep, which is often disrupted by pain. [25]

In a study conducted Doxepin rinse was generally well accepted by patients with oral mucositis. Taste was acceptable and discomfort / burning with use was minimal. These findings were in contrast to typical complaints of taste and discomfort/burning associated with topical application of local anesthetics. Some patients reported sedation after use, likely due to systemic absorption.

Antidepressants for smoking cessation : There are two theoretical reasons to believe antidepressants might help in smoking cessation. Nicotine withdrawal may produce depressive symptoms/ precipitate a major depressive episode and antidepressant drug may relieve these.

In this study, the antidepressant buproprion prescribed for 7 weeks was found to be effective in increasing the rates of abstinence from smoking, and was well tolerated.[26]

Nicotine may have antidepressant effects that maintain smoking and antidepressants may be a substitute for this effect. Alternatively, some antidepressants may have a specific effect on neural pathways by blocking nicotine receptors.

The antidepressants, bupropion and nortryptiline aid long term smoking cessation but SSRTs do not. The evidence suggests that mode of action of bupropion and nortriptyline is independent of their antidepressant effect and they are of similar efficacy to nicotine replacement.

Adverse effects : Adverse effects at lower doses are rare. The Anticholinergic effects include dry

mouth, bad taste, constipation, epigastric distress, urinary retention, blurred vision and palpitation. Other effects may be Sedation, mental confusion and weakness, increased appetite and weight gain. Postural hypotension in older patients. Cardiac arrhythmias in patients with ischemic heart disease. Nausea and headache seen in patients on venlafexine.

Drug Interaction : It has been reported that sub analgesic doses of antidepressant drugs potentiate the action of morphine. Chronic TCA administration modifies opiod receptor densities and increases endogenous brain opiod levels. TCAs therefore enhance endogenous opiod effects and act synergistically with opiods in providing pain relief.

Caution should be exercised in the administration of TCS esp. in patients with history of cardiac disease .A potentially serious outcome may accompany overdosing as well as combination with other drugs such as antihistamines, beta blockers ca channel blockers, SSRI,anticonvulsants . TCAs potentiate directly acting aympathomimetic amines (in cold and asthma remedies).Adrenaline containing LA should be avoided, TCAs potentiate CNS depressants including alcohol and antihistaminics

Contraindications: urinary retention and narrow angle glaucoma, epileptic patients, cardiovascular and diabetic patients. TCAs increase the risk of upper GI bleeding. Pregnancy category D

Conclusion: Antidepressant drugs have sparked some of the most contentious and long-running battles in the history of medicine. The use of these drugs has rapidly expanded far beyond depression. Antidepressants are neither the evil that many believe, nor the magical solution that many hope but if wisely used, can be a valuable adjunct in the management of many oral conditions as evident in this review article.

References:

1. Antidepressant drug update2006
2. Gray AM, Pache DM, Sewell RD (1999) Do alpha 2 adrenoreceptors play an integral role in the antinociceptive mechanism of action of antidepressant compounds? Eur J Pharmacol 378 (2):161-168.
3. Ogata N, Yoshii M ,Narahashi T (1989)psychotropic drugs block voltage gated ion channels in neuroblastoma cells .Brain Res 476(1):140-144.
4. Gerner P,Haderer AE,Mujtaba M,et al (2003) assessment of differential blockade by amitriptyline and its N-methyl derivative in different species by different routes. Anesthesiology 98 (6):1484-1490.
5. Nakashita M,Sasaki K,Sakai N,et al (1997),effects of tricyclic and tetracyclic antidepressants on the three subtypes of GABA transporter.Neurosci Res 29(1) :87-91.
6. Abdel salam OM,Baiuomy AR ,Arbid MS (2004) Studies on the anti-inflammatory effect of Fluoxetine in the rat .Pharmacol Res 49 (2) :119-131.
7. Merskey H,Bogduk N,editors.classification of chronic pain,task force on taxonomy,international association for the study of pain.2nd edition seattle:IASP press;1994.
8. Feinmann C ,psychogenic facial pain: presentation and treatment.j psychsom res 1983;27:403-10
9. Sharav Y ,Singer E,Schmidt E,,et al,the analgesic effect of amitryipltyline on chronic facial pain. Pain 1987;31:199-209
10. Robert G Godfrey,a guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes, Arch intern med ,1996;156:1047-1052
11. Graff –Radford SB ,Solberg WK Atypical odontalgia. J Craino mandib Disord Facial Oral Pain 1992;6:260-266
12. Forssell H,Tasmuth T,Tenovuo O, et al (2004) Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial . j orofac pain 18 (2) :131-137.
13. Rizzatti barbosa CM, Nogueira MTP,de Andrade ED et al ,clinical evaluation of amitriptyline for control of chronic pain caused by

temporomandibular joint disorders J Craniomandib Pract 2003;21:221-5
14. O.Plesh, D.Curtis, J. Levine, W.D.Mccall JR, Journal of Oral Rehabilitation 2000, 27; 834-841.
15. Med Oral Patol Oral Cir Bucal. 2008(to be confirmed)
16. Adelman LC,Adelman JU,Von Seggern R ,et al (2000) Venlafaxine extended release (XR) for The Prophylaxis of migraine and tension type headache : a retrospective study in a clinical setting . Headache 40 (7):572-580
17. Brown GR. Herpes Zoster: Correlation of age, sex, distribution, neuralgia and associated disorders. South med j 1976;69:576-578
18. Watson CP, Vernich L, Chipman M ,Reed K. Nortryptiline versus amytryptiline in post herpetic neuralgia ; randomized trial. Neurology 1998:51:166-171
19. Rowbotham M, Harden N, Stacey B,etal. Gabapentine for the treatment of post herpetic neuralgia:a randomized control trial. JAMA 1998;280:1837-42.
20. Jeffrey P Okeson Bell's Orofacial pain sixth ed pg 493
21. Gorsky M, Silverman S Jr, Chin h. Clinical characteristics and management outcome in the burning mouth syndrome. An open study of130 patients. Oral Surg Oral Med Oral Pathol 1991, 72:192-195.
22. Rozen TD, Relief of anesthesia dolorosa with gabapentine. Headache1999:39;761-762
23. Orofacial pain and headache ,Yair Sharav,Rafael Benoliel, Pharmacotherapy of chronic orofacial pain; pg 382
24. Semenchuk MR, Sherman S, Davis B (2001) double blind, randomized trial of bupropion SR for the treatment of neuropathic pain. Neurology 57 (90):1583-1588
25. Martin S. Greenberg, Michael Glick, jonathan A.Ship "Burket's Oral medicine eleventh edi pg-188.
26. Hurt R, Sachs D, Glover E, Offord K, Johnston J, Dale L, Sullivan P, et al. A comparison of sustained-release bupropion and placebo for smoking cessation, New England Journal of Medicine. 337:1195-202. October 23, 1997.

Conflict of interest: None
Funding: None