"Go mór i mbéal an phobail" – antidepressants and their effects on the mouths of the public.

Mairéad Kelly

Introduction

In recent years, the treatment mechanisms at the disposal of the treating practitioner for mental illness have evolved greatly. The most significant of these for the dental clinician is the use of antidepressant medications which have both direct and indirect implications for dental treatment. It is therefore imperative that the dentist is confident in the management of these patients and the particular set of complications they may present with.

Given the high incidence of these disorders, it is of the utmost importance that the dental practitioner is equipped with the required skillset to adequately manage these patients, and provide them with lifelong holistic care that takes their mental disorder and its implications for treatment into consideration. In 2004, depression was found to be the fourth leading cause of disease burden worldwide and the reported prevalence of depressive episodes found in this study was 16 per 100,000 per year for males and 25 per 100,000 per year for females (Üstün et al, 2004).

On a European Scale, a study including rural and urban areas within Ireland, Spain, the UK, Norway and Finland demonstrated a prevalence of 8.56% of depressive disorders within a 12-month period (Ayuso-Mateos et al, 2001). Due to the high prevalence of depressive disorders in the general population, the dental practitioner is likely to encounter patients suffering from these conditions. In addition to this, the prevalence of depressive disorders in younger age groups has become apparent in recent years. In particular, three quarters of all mood disorders manifest by the age of 24. It is therefore of the utmost importance that the dentist is aware of the implications of these conditions and their management for the dental health of the patient. (Kessler et al., 2005).

Ultimately, a history of a common mental disorder should affect a dentist's management of a patient for a host of pertinent reasons; depressive disorders have frequently been associated with poor oral health, with various studies showing links between depressive disorders and caries, periodontal disease, tooth substance loss and tooth erosion (Delgado-Angulo et al., 2015; Khambaty and Stewart, 2013; Anttila et al., 2001). Furthermore, independent of this increase in dental pathology, patients with mental illness may have an exacerbated perception of dental pain and thus a greater incidence of dental phobia (Kisely, 2016).

The international classification of mental diseases (ICD-10) breaks down mental diseases into various subcategories and the disorders that are the main focus of this review (depression, generalised anxiety disorder and panic disorder) are categorised within this as common mental disorders.

Taking the above factors into consideration, it is apparent that an increased incidence of pathology in the dentition, compounded by dental phobia preventing routine dental examination makes care for these patients both more complex and more urgent. Correct identification of these patients as being at a higher risk of developing dental pathologies, and adaptation of treatment plans to allow consideration of this allows for a more comprehensive approach to patient care.

The treatment of mental illness and its oral implications

Mental health disorders, such as depression and anxiety, are managed using a variety of treatment modalities, the most significant of which to the dental practitioner being pharmacological treatment. Since various antidepressant medications are available, the pharmacological agent is selected based on the patient's symptoms and the side effects profile of the drug. In 75% of cases, antidepressant therapy is an effective treatment modality, and therefore is encountered with relative frequency by dentists (Agency for Health Care Policy and Research, 1993).

The major medications prescribed for depressive disorders include selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), and atypical antidepressants (Snow et al., 2000). SSRIs are also commonly prescribed medications for panic and anxiety disorders (Bandelow et al., 2013).

TCAs were previously the first line drug for the treatment of depression for over a decade, and are still widely in use today (Goldman et al., 1999; Williams et al., 2000).
The SSRI class of drugs are currently the first line of pharmacological treatment for both depressive disorders and panic disorders (Majeroni & Hess, 1998; Kasper & Resinger, 2001). However, although the side effects associated with SSRIs are substantially less debilitating than those of the TCAs, they do nonetheless exhibit some important side effects that may affect the dental practitioner (Edwards and Anderson, 1999) (Spigset, 1999).

The atypical antidepressants have been found to be equally effective as the SSRIs and are also considered first line drugs for mild to moderate depression (Horst and Preskorn, 1998).

The major orofacial side effects of TCAs, SSRIs and atypical antidepressants are outlined in table 2 below. The effects and implications for dental practitioners of each of these drugs is the main topic of interest in this literature review.

Orofacial implications and dental management

A significant number of the drugs discussed in this review have anticholinergic or sympathomimetic effects. Although necessary for the management of depressive and panic disorders, these systems play a major role in the proper functioning of the body and it is therefore unsurprising that they can cause a wide range of side effects.

Pathophysiology

Throughout the literature, the most frequently cited oral implication of antidepressant use is xerostomia, which is defined as a subjective alteration in salivary flow (Saleh et al., 2015). Saliva serves many functions in the oral environment, including moistening and lubricating, taste and smell, digestion, protection of the oral mucosa and oesophagus and tooth protection (Dawes et al., 2015). The TCAs decrease salivary flow by blocking the effects of acetylcholine on muscarinic M3 receptors, which in turn decrease parasympathetic stimulation and decrease stimulation of the salivary glands (Del Vigna de Almeida et al., 2008). SSRIs and atypical antidepressants have sympathomimetic effects. It has been suggested that

ICD-10 Diagnosis	Definition
Depression	A depressive episode, with three typical symptoms of depression and at least four common symptoms where the minimum duration of the depressive episode is at least two weeks. - A depressive episode is defined as depressed mood, loss of interest, and reduced pleasure and energy, leading to increased fatigability and decreased activity
Generalised Anxiety Disorder	Generalised and persistent anxiety, but not restricted to or even strongly predominating in any particular environmental circumstances
Panic Disorder	Panic disorder is defined as a complex mental illness in which a person experiences recurrent and unexpected panic attacks which are not associated with any external event or situation

Table 1. ICD- 10 Classification of mental diseases

this increase in stimulation of the sympathetic system acts on central nervous system adrenoreceptors and indirectly acts on protein secretion of noradrenaline. This in turn inhibits saliva secretion by the salivary glands (Del Vigna de Almeida et al., 2008).

Salivary glands, which are controlled exclusively by neurotransmitters, consist of epithelial cells that excrete fluid and exocrine proteins that serve various functions intraorally. Antidepressant drugs affect the muscular veins and myoepithelial cells, which directly influence the blood circulation of glandular tissue (Sreenby and Schwartz, 1986; Vissink et al., 1992). As such, anticholinergic medications and those that alter adrenergic stimulation of the glands change the composition of the saliva that is secreted as well as decreasing its volume. It has been reported that patients find the change in salivary secretion and composition caused by anticholinergics to be more debilitating than those changes caused by other mechanisms (Vissink et al., 1992).

In addition to this, the reduced resting salivary flow impairment has been seen to return to normal range upon cessation of medication. Interestingly, these medications exhibit a dose-response relationship – the greater the dose of the drug, the more severe the side effects. TCAs exert the greatest xerostomic effect, due to their anticholinergic action (Del Vigna de Almeida et al., 2008) (Hunter and Wilson, 1995). It is uncertain whether it is the decrease in quantity or quality of the saliva that causes patients to complain of the symptoms of dry mouth, although studies suggest that fewer salivary mucins within the saliva secreted is the primary cause of discomfort related to xerostomia (Anttlia et al., 1998).

Saliva is a key component in the mechanisms by which taste occurs. It provides the fluid in which food components and tastants are dissolved and carries these to the taste buds to allow the sensation of taste. A dry oral environment can cause damage to the taste buds, increasing their threshold for taste (Matuso, 2000). Given that dysguesia is another reported side effect of many antidepressant medications, taste sensation in these patients can be significantly altered.

Treatment

Treatment of xerostomia experienced by patients can be achieved by several mechanisms, many of which can be utilised concurrently. Given the potential for medication interaction with antidepressants, prescription of medications such as pilocarpine, which is a parasympathetic stimulant, are inadvisable. Although these medications can successfully be used in the treatment of patients experiencing dry mouth due to other aetiological factors (Saleh et al., 2015), their mechanism of action precludes their use in the treatment of those receiving antidepressant therapy. Therefore, the most effective management of xerostomic symptoms is by use of local salivary substitutes.

Although plain water is an effective salivary substitute in many cases, salivary substitutes containing components such as carboxymethylcellulose (CMC), mucins, xanthan gum, hydroxyethylcellulose, linseed oil or polyethylene oxides give a higher viscosity and therefore greater mucosal protection (Vissink et al., 2010) (Hahnel et al., 2009). Such agents have no known interaction with antidepressant medications and can provide significant relief from the sensation of a dry mouth that is the presenting complaint of many patients.

Pathophysiology

The presence of fermentable carbohydrates in the oral environment is one of the primary aetiological factors of dental caries. Saliva's function in removing debris and the food bolus from the oral cavity is compromised in those with decreased salivary flow, regardless of the aetiology of the dry mouth. Due to prolonged retention of sugars containing fermentable carbohydrates, the caries risk in this cohort of patients is elevated (DaSilva et al., 2011).

Saliva functions as a buffer thanks to the presence of bicarbonate ions that neutralise acid in the oral environment and in the oesophagus following deglutition. Furthermore, carbonic acid, formed by the protonation of bicarbonate ions, reacts to form water and carbon dioxide. This reaction is catalyzed by carbonic anhydrase VI, which is also contained in the saliva (Kivela et al., 1999). This provides protection against acid attack orally, and is a protective factor in patients who are at risk of dysplastic change in the oesophagus due to gastro-oesophageal reflux disease. Salivary mucins may also help to replenish the lining mucous layer in the oesophagus (Sarosiek and McCallum, 2000; Kongara & Soffer, 1999).

Specific Compound	Xerostomia	Dysguesia	Stomatitis	Gingivitis	Glossitis	Tongue Oedema	Bruxism	Sialadenitis	Others
TCA									
Amitriptyline	Yes	Yes	Yes	No	No	Yes	No	Yes	No
Clomipramine	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Oral Ulcers, Dysphagia
Desipramine	Yes	Yes	No	No	No	Yes	No	Yes	Facial Oedema
Doxepin	Yes	Yes	Yes	No	No	No	No	No	No
Imipramine	Yes	Yes	Yes	No	No	Yes	No	Yes	Facial Oedema
Nortriptyline	Yes	Yes	Yes	No	No	Yes	No	Yes	Facial Oedema
Protriptyline	Yes	Yes	Yes	No	No	Yes	No	Yes	Facial Oedema
Tripramine	Yes	Yes	Yes	No	No	Yes	No	Yes	Facial Oedema
SSRI									
Paroxetine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Dysphagia
Sertraline	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Dysphagia, Gingival Hyperplasia
Flovoxamine	Yes	No	Yes	Yes	Yes	No	No	No	No
Fluoxetine	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Citalopram	Yes	Yes	Yes	Yes	No	No	Yes	No	No
Atypical									
Bupriopion	Yes	Yes	Yes	No	Yes	No	Yes	No	Dysphagia
Maprotiline	Yes	Yes	Yes	No	No	No	No	Yes	Dysphagia
Mirtazepine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Facial Oedema
Nefazodone	Yes	Yes	Yes	Yes	Yes	No	No	No	Oral Ulcers
Trazodone	Yes	Yes	No	No	No	No	No	No	Sinusitis
Venlafaxine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Dysphagia

Table2 – the main orofacial effects of Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors and Atypical Antidepressants

The mechanism by which caries cause demineralisation of the dental hard tissues is by the production of bacterial acidic metabolites (Stookey, 2008). When patients who are taking antidepressant medications experience a lower quantity of saliva, this buffering effect of the saliva is diminished, along with its other protective effects.

The epidemiology of dental decay is typically measured by the number of decayed, missing and filled teeth in the dentition, abbreviated to DMFT. Many studies have investigated the relationship between dental caries and mental illness, with a wide range of results and conclusions. However, there is sufficient evidence to support a positive correlation between the factors. Those with depression and anxiety do indeed have an increased risk of developing dental caries, more specifically having a higher DMFT value than the control cohorts (Anttila, et al., 2001; Delgado-Angulo et al., 2015; Kruger et al., 1998; Shah et al., 2012).

Treatment

With the increased DMFT scores observed in patients with mental illness as well as the increased caries risk due to decreased salivary flow and dry mouth, caries prevention should be a priority for the dental practitioner in these cases. The use of oral hygiene education, home oral hygiene maintenance, increased fluoride use, and antimicrobial mouthwash use to decrease this caries risk have all been shown to be effective (Friedlander and West, 1991). More frequent dental recall times, examination and interventions such as scaling and topical fluoride application will also ensure the maximisation of oral health in this patient cohort (Friedlander and Mahler, 2001).

Of significant concern to dental practitioners is the interaction between antidepressant medications and those prescribed by the dentist. Given both the broad range of medications prescribed by the dentist and the broad range of antidepressant medications, the propensity for drug interaction is vast.

Commonly prescribed antibiotics in the dental setting include the macrolide group, of which erythromycin and clindamycin are members. These antibiotics are the first line of treatment for dental infection for patients with an allergy to the penicillins. Azole antifungal medications are used in the treatment of candida infections and are commonly prescribed by dental practitioners. Both the macrolides and the azoles are metabolised by the CYP450 enzymes in the liver, but it is their inhibitory effects on these enzymes that pose a risk to the patient. Benzodiazepine medications are also metabolised by CYP450 and so its inhibition can significantly affect the bioavailability of the benzodiazepine group (Hersh, 1999). By increasing the bioavailability of benzodiazepines, this interaction could result in overdose and CNS depression.

Post-operative pain in dentistry often results in the prescription of analgesics. When this pain is severe, the prescription of opioid analgesics such as codeine, hydrocodone or tramadol is quite common. However, prescription of opioids with CNS depressants or monoamine oxidase inhibitors has been shown in some studies to cause a life-threatening interaction (Haas, DA., 1999). The use of local anaesthetics is generally considered safe, although care should be exercised with those patient receiving treatment by medications affecting the adrenergic system. Adrenaline within a local anaesthetic cannot bind to alpha-1-adrenergic receptors in patients receiving medications that block alpha-1- adrenergic receptors. The adrenaline then binds to alpha-1-adrenergic receptors instead causing vasodilation and resulting in hypotension (Keene et al., 2003). Therefore, consideration should be given to the medications being taken by the patient prior to administration of local anaesthetics containing adrenaline in their formulations or use of haemostatic agents containing adrenaline.

Conclusion

Due to the prevalence of depressive disorders in the general public, the dental practitioner is likely to encounter patients suffering from these conditions. Since anti-depressant drugs can cause an array of side effects, it is important for the practitioner to understand the pharmacology and mechanisms of action of these treatments.Xerostomia, increased caries risk, orthostatic hypotension and interactions with other drugs mean that these medications can be detrimental to oral health and can result in adverse reactions in dental practice that can be potentially life threatening.

The impact of antidepressant use on patient management highlights the importance of obtaining a thorough medical history. Disclosure of a history of mental illness and antidepressant use on a patient's behalf may be difficult and therefore, a positive relationship with the practitioner, exhibiting a non-judgemental attitude and a supportive environment is also of the essence. These patients are inevitably encountered in practice with great frequency and so, knowledge of these medications and their orofacial manifestations and implications for treatment are imperative for the dental practitioner.

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