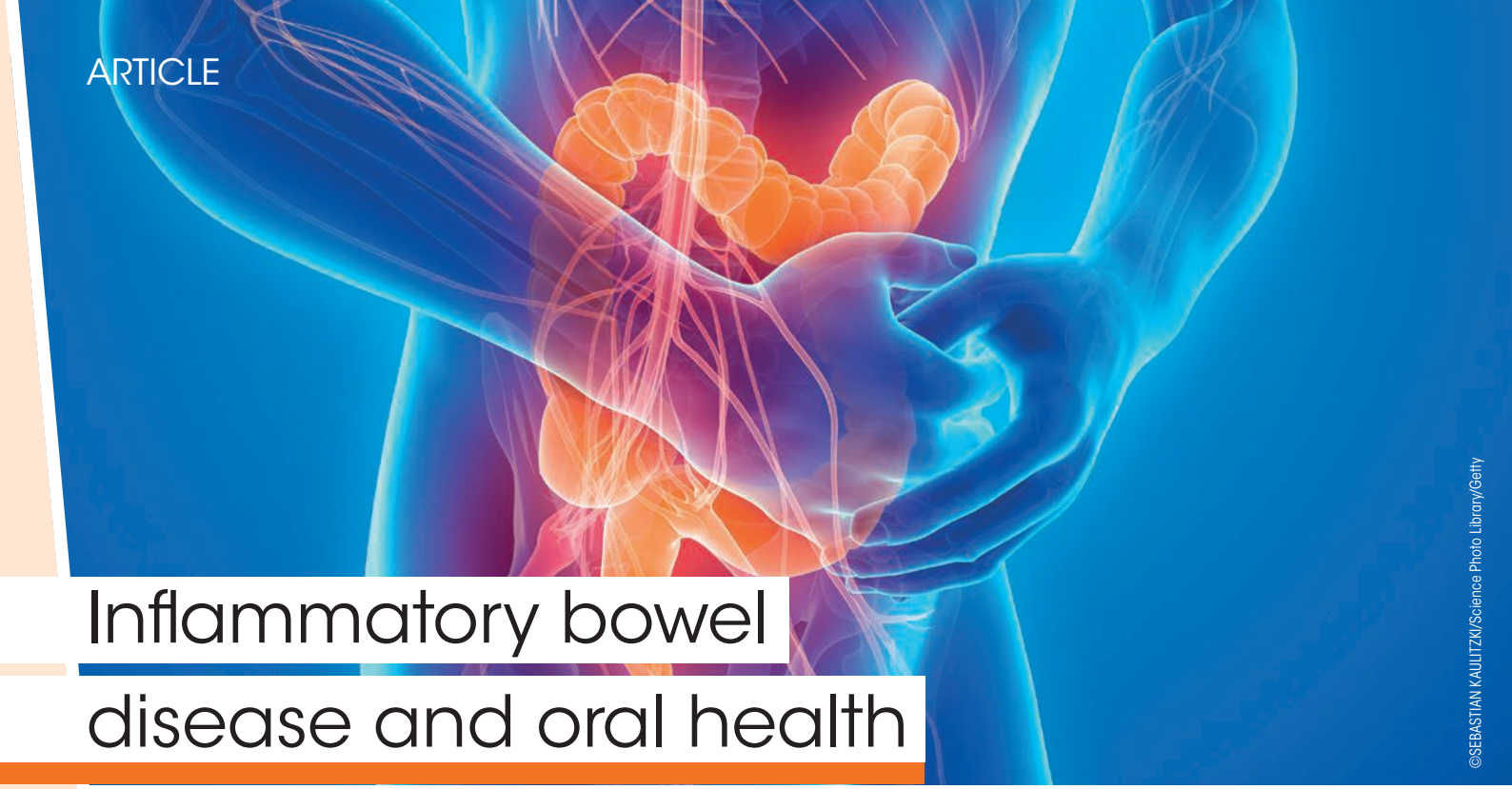

Inflammatory bowel disease and oral health

J. S. Chandan[1] and **T. Thomas**[1] summarise the treatments for inflammatory bowel disease (IBD) and how anti-inflammatory medications can have side effects that affect the oral cavity.

Inflammatory bowel disease (IBD) mainly comprises of two separate inflammatory conditions: Crohn's disease (CD) and ulcerative colitis (UC). The aetiology of these conditions is still being explored with current evidence pointing towards a combination of environmental and genetic components. However, the pathophysiology is understood as a cytokine driven inflammatory response. There is significant association between IBD and dental conditions such as dental caries, other infections and periodontitis. Anti-inflammatory medications such as 5 aminosalicylic acid (5ASA), steroids and biological therapies are the treatment of choice for these chronic conditions, dependent on aetiology. Therefore, this article aims to educate dentists regarding possible implications IBD and its treatment can have for clinical practice and future research.

Introduction

Inflammatory bowel disease (IBD) is an umbrella term mainly comprising of two separate medical conditions: Crohn's disease (CD) and ulcerative colitis (UC). They are chronic inflammatory conditions affecting the digestive system that can lead to acute flare-ups of the respective conditions. CD can affect any part of the GI system (most commonly the small bowel, whereas UC only affects the large bowel.[1]

The incidence of IBD is beginning to stabilise in Europe with about 2.2 million people suffering from the condition.[2] In the UK it is estimated at least 115,000 people have CD and around 146,000 have a diagnosis of UC.[3] It is a condition that is most commonly diagnosed during childhood or early adolescence.[4]

Risk factors involved in IBD

IBD is thought to result from inappropriate and ongoing activation of the mucosal immune system facilitated by defects in both the intestinal epithelium and mucosal immune system.[5] There are both genetic and environmental factors implicated in the aetiology of IBD.[6] Although traditionally associated with the developed world, recent epidemiological studies suggest an increasing incidence in rapidly developing countries, especially in South-East Asia.[7] In addition, the increased risk of IBD in the immigrant populations in the West suggests environment has a role in the development of IBD.[8]

Genetic

Detailed genetic mapping has identified specific genetic changes on chromosome 16 carried in families which appear linked to CD, however no significant changes have been mapped as of yet to UC.[9,10] Specifically, variants of the NOD2 gene provide the strongest association with susceptibility to CD. NOD2 plays a key role in regulating the gut mucosal barrier involving, specifically, the microbiota, as well as the related response by the innate and adaptive immune system. The IBDchip European Project showed NOD2 has been implicated in ileal location colitis with stenosing and penetrating disease behaviour.[11] A genome wide association study has also identified a strong link between the IL23R gene and CD.[12] The gene in particular codes for interleukin 23 that plays a role in regulating innate immunity within the intestine.[13]

Cigarette smoking

Unusually, cigarette smoking is associated with decreased rates of incidence of UC and has been associated with protective features to prevent further flare-ups of the condition[14-19] such as relapses,[20]

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hospitalisations[21] and colectomies.[22] Also, complications of the condition are reduced in those who do smoke. This raises the concept of encouraging smoking to prevent adverse events occurring. However, there is a plethora of evidence that suggests that smoking has adverse effects on overall morbidity outcomes. In particular, it can increase failure in dental implants,[23] increase the risk of oral cancers and increase the incidence of dental infections.[24] Guidelines advocate smoking cessation in UC patients. On the contrary CD patients who smoke have a more severe disease course and can increase the incidence of CD with further complications.[18,25-27] In fact, smoking cessation can provide a 65% reduction in the risk of relapse versus smokers. This is comparable to the reduction of risk attributed to immunosuppressive therapy.[28]

Other environmental risk factors

In observational studies, appendectomies appear to provide a risk reduction in the development of UC.[29] Oral contraceptives statistically significantly increased the risk for developing CD and appeared to increase the risk of UC.[30] The other important environmental factor playing on the development of IBD is diet control. The greatest association appears to be between increased sugar intake and developing IBD.[31] This is especially important to note considering increased sugar intake can lead to the development of dental caries.[32,33] Secondly, increased sugar content will be a contributing factor to diabetes which already has a causal link with periodontal disease.[34]

Pathology of IBD

The pathophysiology behind IBD has been under intense research scrutiny for the last decade, and much of it is still unknown. However, it is clear that it consists of complex interplay between genetic influences, environmental factors, microbial flora and the host immune system.[35] The dysfunction of the innate and adaptive immune system is at the centre of the inflammatory process. The innate immune system is the immediate nonspecific response system of the body with response times ranging from minutes to hours. It consists of the epithelial cells, neutrophils and natural killer Tcells among other cells. The pattern recognition receptors (PCR) such as toll-like receptors and NOD-like receptors recognising valid pathogen associated molecular patterns (PAMPs) are one of the main triggers for this system. However, mutations in underlying genes such as NOD2, that plays a key role in immune tolerance, result in inappropriate immune responses. In addition, it can lead to inappropriate Th1 pathway stimulation due to decreased inhibition of the TLR2 stimulation.[36] Other important factors affecting the innate immune system in IBD include autophagy defects due to gene mutations such as in the ATG16L1 gene, which has been implicated in CD.

The adaptive immune system is the specific immune response system, consisting of Bcells and Tcells among others. There have been theories that there are two distinct adaptive immune system pathologies driving CD and UC. It was suggested that the IL12 cytokine stimulation resulting in Th1 mediated upregulation and thereby IFNY could be one of the main players in CD. Likewise, in the case of UC, Th2 mediated inflammation reaction was thought to be a key player. However, recent research has described mixed cytokine profiles in UC, and therefore, it is clear that further research needs to be performed to investigate the specific roles of Th1 and Th2 in IBD.[37]

Oral presentations of IBD

Current literature suggests that up to 35% of IBD patients will have an extra-intestinal manifestation.[38] The oral cavity could potentially be affecting up to 5-50% of patients. The wide range is due to the non-specificity of oral symptoms. However, broadly speaking, this population tends to be made up of CD patients, with children being affected more than adults.[39] Older children and adolescents in particular are vulnerable to oral CD manifestations.[40] One of the reasons why it is important to be aware of the signs and symptoms of CD is due to the hypothesis that oral inflammation may precede intestinal manifestation of disease.[41]

In a tertiary centre case-control study conducted in Portugal, consisting of 113 patients with previously diagnosed IBD and 58 healthy controls, there was a significantly increased prevalence of oral symptoms when compared with the control that did not have IBD (54.9% vs. 24.3%, P = 0.011).[42] Oral symptoms were also present in a greater proportion within the active phase cohort than in the remission cohort (70.6% vs. 52.1%, P = 0.001). Moreover, aphthous ulcers had a substantially increased presence within the active phase when compared with remission (35.3% vs. 4.2%, P <0.001).

Signs/symptoms of oro-facial IBD

Signs and symptoms that manifest with IBD are overwhelmingly that of CD. The most common sites involved are the lips, buccal mucosa and gingiva.[43] Orofacial CD can present with aphthous ulcerations, angular cheilitis, and cobblestoning with or without oedema of the lips. Figures 1 and 2 demonstrate some of these oral manifestations of CD. Mucosal tags in the gingiva should also be treated with suspicion. The buccal mucosa can also contain abscesses, alongside cobblestone features and ooedema. Pyostomatis vegetans is a rare condition that could indicate the presence of CD as well as UC. It is characterised by dramatic erythematous thickened mucosa with widespread erosions. Case reports[44,45] have indicated that oro-facial fistulae can be another rare outcome of IBD often presenting as a discharging abscess on the face. The aetiology of these fistulae is unclear as there appears to be overlap with granulomatous oro-facial disease.[46]

'SIGNS AND SYMPTOMS THAT MANIFEST WITH INFLAMMATORY BOWEL DISEASE ARE OVERWHELMINGLY THAT OF CROHN'S DISEASE. THE MOST COMMON SITES ARE THE LIPS, BUCCAL MUCOSA AND GINGIVA.'

Conditions associated with IBD

Current research suggests that IBD patients are more likely to undergo dental procedures than a healthy cohort.[47] In particular, CD patients were 1.18 times more likely to undergo dental treatment compared to healthy controls (P <0.000). Removable dentures (+65%), front teeth fillings (+52%), and endodontic treatment (+46%) in particular were more prevalent in the CD cohort. Similarly, UC patients were 1.09 times more likely to undergo dental treatment compared to health controls (P <0.005). In particular, these patients were 1.33 times more likely to have fillings in canines and

incisors than the healthy controls (P <0.001). The impact of IBD on oral health is thus well described. However, the exact nature of this relationship is unclear. The underlying inflammatory changes in IBD plays a role in poor oral health, however, the link is not causal aside from in the case of specific oral complications of IBD. The associations mainly appear to be linked to the development of dental caries, periodontal disease and other loosely related conditions through other risk factors associated with the development of IBD, such as high sugar intake.

Dental caries/infection

There appears to be a significant association with tooth caries and oral ulcers in IBD compared to the normal population.[48] A case control study consisting of 110 participants[49] identified children with IBD had statistically significantly higher rates of decayed, missing and filled teeth (dmft) (2.95 vs 0.91). IBD patients also have increased rates of lactobacilli and streptococcus mutans found in their oral cavity contributing to caries.[50] The reasoning behind why these increased rates of caries and infections are not clear, however, proposed arguments include salivary components (increased bacterial concentrations), oral hygiene and diet.[51,52] As discussed above, a risk factor for patients developing IBD is the increased sugar intake that can be associated with further infection.

Periodontal disease

The association between IBD and periodontal disease is starting to emerge in recent literature.[53] Due to the inflammatory nature of both disorders, it is hypothesised that underlying IBD can trigger a raised basal cytokine response that can induce periodontal disease. Several case control studies have been conducted to explore this relationship further. A German study[54] identified that twice as many patients with IBD, compared to those without IBD, had clinic attachment loss >5 mm, however, mean loss was not statistically significant. However, since then further prospective trials have identified that IBD patients have higher provenances of periodontal disease, deeper pocket depth and more clinical attachment loss.[55,56]

Malnutrition

Malnutrition is very prevalent within the IBD population. Literature has previously estimated this number to be almost one in four outpatients, and almost nine out of ten inpatients.[57] This could be due to direct factors such as loss of normal resorptive mechanisms and higher nutritional requirements due to the inflammatory process. Indirect factors can also play a role and this can be due to reduced intake and side effects of concurrent medication. Particularly in CD, involvement of the small bowel can hinder absorption of vital nutrients. Iron malabsorption can occur if the duodenum and upper jejunum is affected, and this can manifest as angular cheilitis and glossitis.[58] On a systemic level, low iron gives rise to the microcytic hypochromic anaemia picture. Involvement of the terminal ileum can result in folate and B_{12} deficiencies causing painful glossitis and stomatitis, among others. This manifests as macrocytic anaemia. Other nutrients prone to deficiencies include magnesium, potassium, vitamin D, selenium and zinc. Malnutrition of these micronutrients often results in non-specific oral lesions.

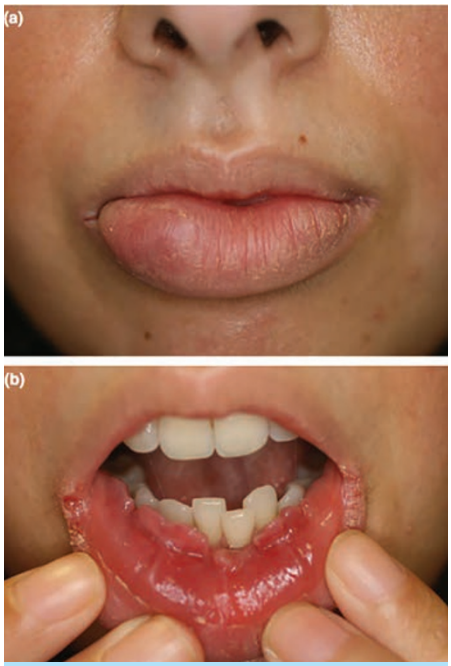

Fig. 1 Oral Crohn's disease: macrocheileitis (a), angular stomatitis and mucosal tags (b). Reproduced with permission from Katsanos K H *et al.* Non-malignant oral manifestations in inflammatory bowel diseases, *Aliment Pharmacol Ther,* 2015; 42, John Wiley and Sons

Medications

The therapeutic route to disease remission in IBD differs slightly between CD and UC. Steroids play an integral role in induction of remission in both conditions. In summary, the NICE-recommended UC pathway[59] (as per individual patient needs) is as follows:

1. 5-aminosalicylic acid (5ASA) therapy such as sulphasalazine or mesalazine
2. Thiopurine therapy (Azathioprine or 6mercaptopurine)
3. Biologic therapy consisting of infliximab/adalimumab.

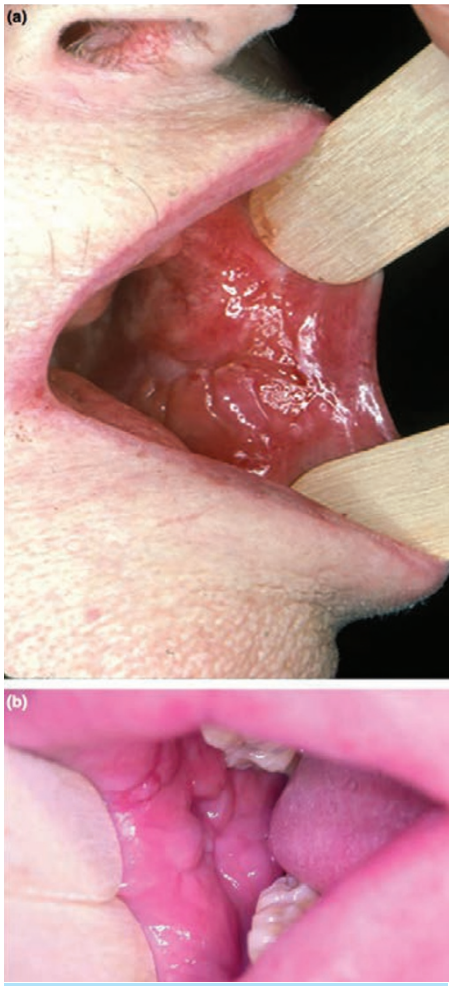

Fig. 2 (a-b) Oral Crohn's disease: cobblestoning and linear ulcers in the buccal mucosa. Reproduced with permission from Katsanos K H *et al.* Non-malignant oral manifestations in inflammatory bowel diseases, *Aliment Pharmacol Ther,* 2015; 42, John Wiley and Sons

Newer monoclonal antibody therapies such as golimumab, vedolizumab and ustekinumab are now in use in specialised cases within tertiary centres.

The corresponding pathway for CD60 (again as per individual patient needs) is as follows:

1. Thiopurine therapy (Azathioprine or 6mercaptopurine)
2. Methotrexate
3. Biologic therapy consisting of infliximab/adalimumab.

In the case of colonic CD, 5ASA therapies may also be used with good efficacy. As the medications overlap largely between the conditions we will explore the dental associations related to these medications. It should be noted that these medications have potent anti-inflammatory and immunosuppressant actions and therefore reduce the body's ability to fight infection, which is an important consideration in an oral health context.

5-ASAs

5-ASAs such as sulphasalazine and mesalazine act as anti-inflammatory medications providing topical relief inside the intestines. They do this by reducing synthesis of inflammatory cytokines and have been used for many years.[61] They are medications that can cause a host of side effects from common ones including nausea, vomiting and GI upset.[62] However, three are of particular importance and interest to dentists. The first being the risk of drug induced agranulocytosis.[63] Agranulocytosis is an acute condition leading to a severe leucopenia where there a reduction in white blood cells affect the way the body can fight infection. Secondly, of interest to the dental profession, 5-ASAs have supposedly caused a few cases of parotitis which is a swelling of the parotid gland similar to mumps but it is unclear whether this was due to the medication or progression of the condition, however, it is still noted as a side effect for the medication.[64] Thirdly, a few patients have noted taste disturbances which may present to the dentist before the doctor.[65]

Purine analogues

Azathioprine and 6mercaptopurine are both purine analogues and widely used immune-suppressants to dampen the immune response in both conditions.[66] Similarly to 5ASAs, these medications can cause an acute leucopenia which can severely impair the body's effect on fighting infection.[67] Secondly, there is a fourfold documented increase in the risk of lymphoma with these medications which can present in the oral cavity.[68,69] It should be noted, however, that there is only a very small absolute increase in the risk of lymphoma occurrence.

Methotrexate

The role of methotrexate in IBD management is rare. However, methotrexate can be used as an effective immune-modulator in inflammatory bowel disease.[70] Of importance to dentists, methotrexate can commonly cause ulcerative stomatitis[71] and recent case reports have identified Epstein-Barr associated lympho-proliferative disorders occurring in the gingiva of patients taking methotroxate, causing gingival ulceration.[72,73]

Biologic anti-TNF agents

Both infliximab and adalimumab are relatively new antibody-based drugs against TNF (tumour necrosis factor), which is a cytokine agent in the body's immune response, upregulated in inflammatory conditions such as IBD. These medications pose fewer adverse effects related to the oral region, however, they are associated with reactivation of latent TB.[74,75] Therefore, it is still worth enquiring about opportunistic dental screenings whether or not these patients have experienced systemic symptoms of TB as it is of public health importance. In addition, as these medications are still relatively new, the long-term risks of them are unknown. Any cause for concern in a patient on biologic treatment should ideally be escalated to the medical team for thorough investigation.

Treatment of oral lesions

The main underlying principle in treating oral lesions in IBD lies in identifying the cause of oral lesions. These could be directly due to IBD, malnutrition or concurrent medication use (as mentioned below).

Oral involvement of IBD revolves around treating the intestinal manifestation of the disease. However, topical and systemic medical treatment modalities are available. Corticosteroid injections can be applied locally to the lesion. In addition, symptomatic relief is available via use of lidocaine 2% in the most severe cases. Less potent treatment modalities take the form of ointments. Evidence shows that topical tacrolimus at relatively low concentrations of 0.5 mg/kg can be potent in oral manifestations of CD.[76]

Other ointment options include the use of 1% hydrocortisone three times daily. Steroid mouthwashes (dexamethasone elixir) are also available for symptomatic relief. These methods of treatment, particularly topical dexamethasone ointments, are effective treatments for refractory aphthous ulcers as well.[77]

Typically, systemic medical treatment is reserved for the most severe of oral cases. Evidence advocating systemic medical treatment to combat oral manifestation of IBD consists largely of low sample size studies. However, it has been shown that combination therapy of steroids and azathioprine can potentially be beneficial.[78] Staines *et al.* 2007[79] suggested that anti-TNF inhibitors can be of benefit in complex oral manifestations such as fistulating oral disease.

Surgical treatment and biopsy

Surgical modalities for treatment of oral manifestations of IBD are used in cases where complications have developed such as fistulations and abscesses. In these cases, a combination of maxillofacial surgery and plastic surgery may be indicated. Orofacial surgery is relatively more complex in the IBD cohort. There is evidence to suggest that this cohort is at higher risk of oropharyngeal perforation.[80] Post-operative recovery may also be impaired in these patients due to concomitant use of systemic steroids and potent immunosuppressants.

Diet

Diet is an important factor that can be overlooked in managing oral health manifestations of IBD. An early study[81] identified that strict elimination diets, where a potential trigger in the diet leading to the flare of aphthous ulcer is identified and removed, provide symptomatic relief. The management of diet-related oral manifestations largely represents replacing the vitamin or mineral that is depleted. There are known associations between decreased ferritin levels and oral ulcers, therefore, appropriate replacement would help prevent development.[82]

'A STUDY IDENTIFIED THAT STRICT ELIMINATION DIETS, WHERE A POTENTIAL TRIGGER IN THE DIET LEADING TO THE FLARE OF APHTHOUS ULCER IS IDENTIFIED AND REMOVED, PROVIDE RELIEF'

Take home message

From the literature and clinical experience earlier, there is an evident association between IBD and various dental health conditions. Implications for education, practice and future research should be considered.

Implications for education

Dentists should be aware of the conditions that comprise IBD and their links to dental conditions such as dental caries, periodontitis and other oral infections. Secondly, dentists should be aware of the medications such patients take for the conditions, which in their own right can induce oral signs.

Implications for practice

Dentists should be able to identify oral presentations associated with IBD. Where early

oral signs and symptoms exist, especially in young patients without a medical diagnosis, dentists should be implored to refer patients to their GP for further testing. Evidence has shown that early expert oral investigation in children presenting with these signs can be of great diagnostic benefit.[83] Patients susceptible to eating high amounts of sugar should also be spoken to further in consultation regarding risk factors to do with IBD. Dentists should use dental check-ups as opportunistic screening moments for patients on these medications to ensure they are not getting any oral side effects.

Implications for further research

As this was a review of the available research to educate dentists it did not act to increase the evidence base in this field. There remains many opportunities to conduct audits and investigations, especially regarding oral side effects of medications as this is a particularly under researched area.

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