

# Side Effects Of Steroidal And Non-Steroidal Anti-Inflammatory Drugs On The Oral Cavity.

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**Background and objectives:** The steroidal and Non-Steroidal Anti-Inflammatory drugs (NSAIDs) are widely used classes of medications for their anti-inflammatory and analgesic effects and are associated with the risk of many oral side effects and which might be presented with variable degrees of severity. The main objective of this research was to identify oral side effects that could be associated with using Steroidal or NSAIDs.

**Patients and Methods:** A total number of 82 patients who were attending the teaching clinics at the college of dentistry and were using steroids or NSAIDs participated in this study and they were interviewed and examined clinically for the presence of any abnormal oral presentation. The data were all recorded on a pre-designed questionnaire. The data was expressed as percentage and analyzed statistically using ANOVA and t-test.

**Results:** The data showed that a majority of NSAIDs users complained of gingival bleeding (39%) and Xerostomia (32%), while corticosteroid users complained of fungal infection (50%), gingival inflammation (25%) and other less frequent side effects. Drugs that were associated with the most oral side effects were aspirin, ibuprofen, mefenamic acid and prednisolone.

**Conclusion:** Data analysis showed that many oral side effects might be related to steroidal and NSAIDs. It is important to consider that drugs in general may cause oral side effects at different doses, dosage forms and durations of use and may have a variety of clinical presentation. The dentists have a crucial role in identifying these drug-related oral side effects through their clinical practices in order to provide the proper management for the patients.

**Keywords:** Side effects, steroids, NSAIDs, xerostomia, Ulcers.

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## INTRODUCTION

Steroidal and Non-steroidal anti-inflammatory drugs (NSAIDs) are both prescribed widely for their immunomodulatory, anti-inflammatory and analgesic effect. These drugs, even when they are taken at the prescribed therapeutic dose, they can have the potential to cause both systemic and oral side effects. Adverse effects from medications taken either locally or systemically can have an impact on every area of the oral tissues, some of the most common are xerostomia, ulcerations, burning mouth symptom, gingival bleeding, hyperplasia and lichenoid reactions.<sup>1</sup>

The Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are a class of medications that have analgesic, anti-inflammatory and antipyretic effects.<sup>2</sup> NSAIDs act by inhibiting the production of prostaglandins through inhibiting the activity of cyclooxygenase enzyme (COX), which functions as a homeostatic enzyme in most tissues, this occurs as NSAIDs compete with arachidonic acid (AA) for the COX active site. Following the discovery of COX-2 selective inhibitors, also known as COXIBs, NSAIDs underwent a second generation. These were created to counteract the gastrointestinal tract (GIT) side effects of

conventional NSAIDs. However, the COX-IB revolution quickly came to an end as a result of evidence showing that these drugs were becoming more likely to cause myocardial infarction and stroke, which led to the withdrawal of several COXIBs from the market.<sup>3</sup> Traditional nonselective NSAIDs, that inhibit both COX1 and COX2 enzymes, may have negative side effects, such as gastrointestinal bleeding and the inhibition of muco-protective prostaglandins, when taken at therapeutic doses. The development of selective COX-2 inhibitors, which in contrast to conventional NSAIDs, maintained the gastro-protective effects by sparing COX-1 isoenzyme.<sup>4</sup> A third isoform (COX-3) was discovered in 2002 by Simmons and coworkers. In contrast to other NSAIDs, acetaminophen is known to only have weak inhibitory effect on COX-1 and COX-2 at therapeutic doses. The research by the Simmons group demonstrated that acetaminophen does in fact target COX-3.<sup>5</sup> NSAIDs have been mostly used in dentistry to achieve relief from dental pain and inflammation. Dental tissue damage causes a complex cascade process known as odontogenic pain or dental pain, which is accompanied by a variety of neuronal stimuli as a result of morphologic, neurovascular, and neuroinflammatory reactions. The most typical cause of dental pain in dental practice is caused by pulpal and periapical disease.<sup>2</sup> NSAIDs are either self-medicated as over the counter medication or they are used according to medical prescription for treating pain of inflammatory diseases. Some of the oral side effects that are most commonly attributed to the use of NSAIDs include hyposalivation, burning mouth symptoms, oral ulcerations, angioedema, erythema multiforme, lichenoid reaction, oral mucosal pigmentations and Candida infection.<sup>1</sup> Commonly used NSAIDs include aspirin (Acetylsalicylic Acid) which is mostly used for its antiplatelet effect for the control of Cardiovascular disorder, as prophylaxis and only previously used as a weak analgesic. Common oral side effects as a result of the use of Aspirin include gingival bleeding, ecchymosis, oral rashes, dysphagia, bruising and xerostomia.<sup>6</sup> Ibuprofen is another

commonly used NSAID, used primarily as an anti-inflammatory analgesic and antipyretic agent.<sup>7</sup> Oral side effects that commonly occur from the use of Ibuprofen include Dysphagia, pain or discomfort in the throat and less commonly, gingival bleeding, blistering, xerostomia, erythematous lesions with a purple center, ulcerations, sore throat and swelling.<sup>8</sup> Corticosteroids are also used in dentistry for their anti-inflammatory and immunomodulatory effects, these drugs resemble steroid hormones that are naturally produced by the adrenal cortex in our body and exist as glucocorticoids and mineralocorticoids.<sup>9</sup> The basic mechanism of action of corticosteroids is through interactions with globally expressed intracellular glucocorticoid receptors and control of gene expression.<sup>10</sup> Corticosteroids cause inhibition of cytokine, chemokine, and adhesion molecule production as well as the inhibition of pro-inflammatory cytokines like tumor necrosis factor and interleukin-1 resulting in inhibiting vascular permeability, vasodilation, leucocyte migration and this cause reduced swelling, erythema, plasma exudation and decreased inflammatory pain.<sup>11</sup> Corticosteroids achieve the immunosuppressant effects through alterations to the adhesion molecules and preventing the neutrophils from reaching the site of inflammation, reduction in the level of circulating eosinophils, basophils, monocytes and lymphocytes has also been noted in response to the use of Corticosteroids.<sup>10</sup> The most important uses of corticosteroids in dentistry include treatment of Oral diseases such as (Recurrent aphthous stomatitis, oral lichen planus, erythema multiforme, pemphigus vulgaris, Behcet's disease, central giant cell granuloma, it also has significant uses in endodontics (reduction in pulpal inflammation), orthodontics and oral surgery (After oral surgical procedures, steroids are administered to reduce edema and inflammation) and treatment of Anaphylaxis.<sup>12,13,14</sup> The oral side effects associated with the use of Corticosteroids are numerous, some of the most common include swellings, bruising and slower wound healing due to the

disruption of normal healing mechanisms which involve interference with inflammation, fibroblast proliferation, collagen synthesis and degradation, angiogenesis, wound contraction, and re-epithelialization. There is increased risk of infections particularly oral candidiasis, due to their immunosuppressive effect. A round face or moon face caused by fat deposition on the side of skull, causing Cushingoid features.<sup>15,16</sup> Bone loss and decreased bone density (known as Osteoporosis) is another side effect, this is most likely due to the suppression of the hypothalamic-pituitary-adrenal (HPA) axis in chronic users.<sup>17</sup> GIT side effects are other significant issues, in comparison to using either drug alone, there is a 4-fold increased risk of GI side effects when using NSAIDs and glucocorticoids together. Finally, by inhibiting the hypothalamic-pituitary-adrenal (HPA) axis, glucocorticoids can reduce corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland and endogenous cortisol. In patients with chronic ACTH suppression, abrupt discontinuation or rapid withdrawal of glucocorticoids may result in symptoms of adrenal insufficiency.<sup>18</sup>

Topical corticosteroids are also commonly prescribed in dentistry as triamcinolone which is used for achieving relief from symptoms of mouth sores due to injury and autoimmune lesions as oral lichen planus, oral candidiasis was the most frequently reported oral side effect, with swelling, bruising or discoloration, slow wound healing and itching all being observed less commonly.<sup>19</sup> Prednisolone and Prednisone are also commonly used as a systemic medication for the treatment of severe allergies, inflammatory and auto-immune conditions, and their use was associated with increased risk of infections; additionally, ulcerations; particularly with the adjunct use of an NSAID is another common finding. Bone thinning, bruising and slower wound healing can also be seen less commonly.<sup>20</sup> Hydrocortisone is another example of glucocorticoid drugs, it is the most suitable drug for replacement purposes, as it is a synthetic cortisol, swellings, infections, bruising and osteoporosis are common

findings with its use.<sup>21,22</sup> The aim of the study was to identify the oral side effects that might be related to the use of any drug which belongs to steroidal or NSAIDs.

#### PATIENTS AND METHODS

This study was conducted at the teaching clinics of Dentistry College/Hawler Medical University/Erbil city. The overall sample size included (82) patients who were seeking dental treatment, both male (no=34) and female (no=48) from different age groups who were using steroidal or NSAIDs were enrolled in the study. The age grouping

**Table 1: Age grouping of participants**

	Age range (years)	No. of patients
Child	Up to 16	5
Young adult	17-30	30
Middle-aged adult	31-45	18
Old-age adult	Above 45	29

is shown in (Table 1).

The questionnaire was formulated to include 3 parts: 1. The patient's personal information, including: name, gender, age, address, phone number and chief complaint. 2. Information regarding the use of the medications (Steroidal and/or NSAIDs), including: the name of drug used, dose, dosage form, route of administration, frequency of the dosing and duration of use. 3. And the reasons for using the medication. Finally, the data collection included reporting any oral side effect that is manifested and diagnosed under the supervision of dental professionals which could be associated with the use of any of those two classes of anti-inflammatory drugs. For the purpose of clinical diagnosis, dental mirrors, probe and gloves were used.

A profound medical history was also recorded with each patient and all information was written on the questionnaire papers by the researcher, and any patient using medications other than these two groups of drugs were excluded from the study. Data were evaluated using descriptive

statistics as percentages and mean and were analyzed statistically using ANOVA and unpaired t-test.

**RESULTS**

The results of this questionnaire study showed that the most commonly used

NSAIDs among the patients were aspirin (no=18), ibuprofen (no=18) and mefenamic acid (no=16), diclofenac (no=6), indomethacin (no=4) and their percentages of use are shown in (Figure1).

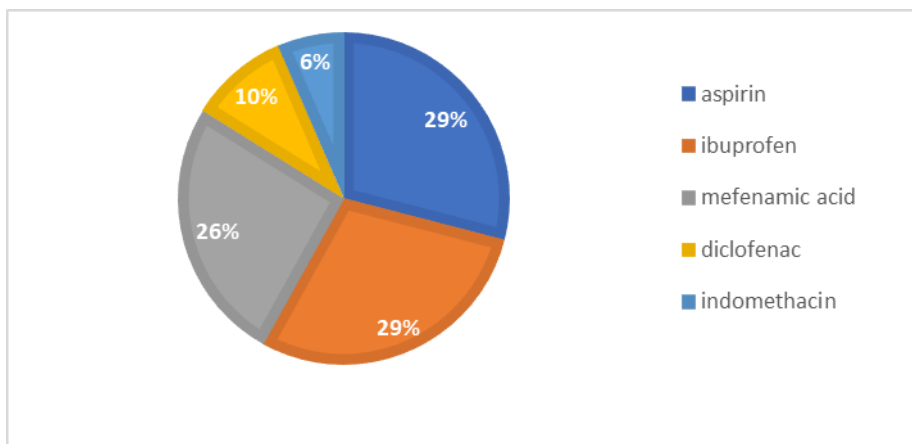


Figure 1: The percentage of commonly used NSAIDs by the patients.

The most common oral side effects that were presented among the users of NSAIDs (no=62), that were investigated in the study, were gingival bleeding (no=24), xerostomia (no=20), taste disorders (no=18), dysphagia

(no=14), ulcers (no=14); which were mostly of aphthous type, ulceration and other less frequent side effects, the percentage for these side effects are shown in (Figure2).

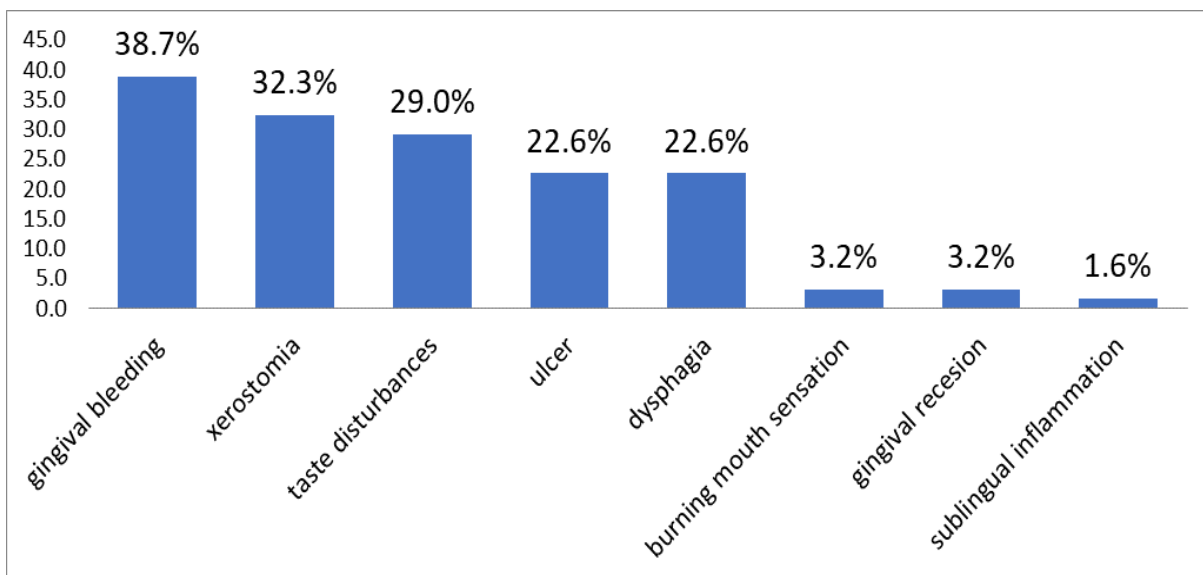
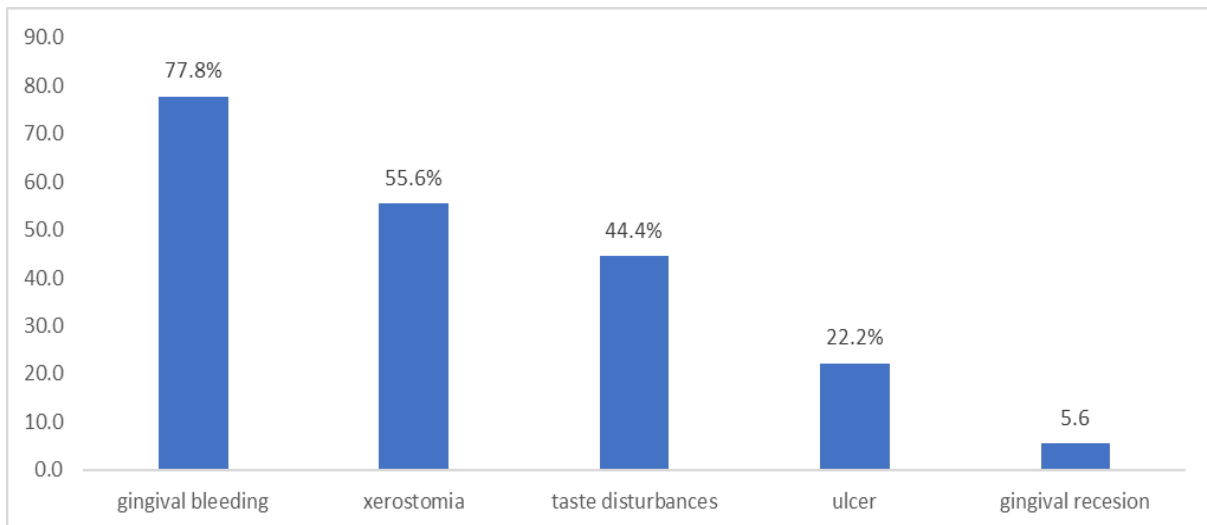


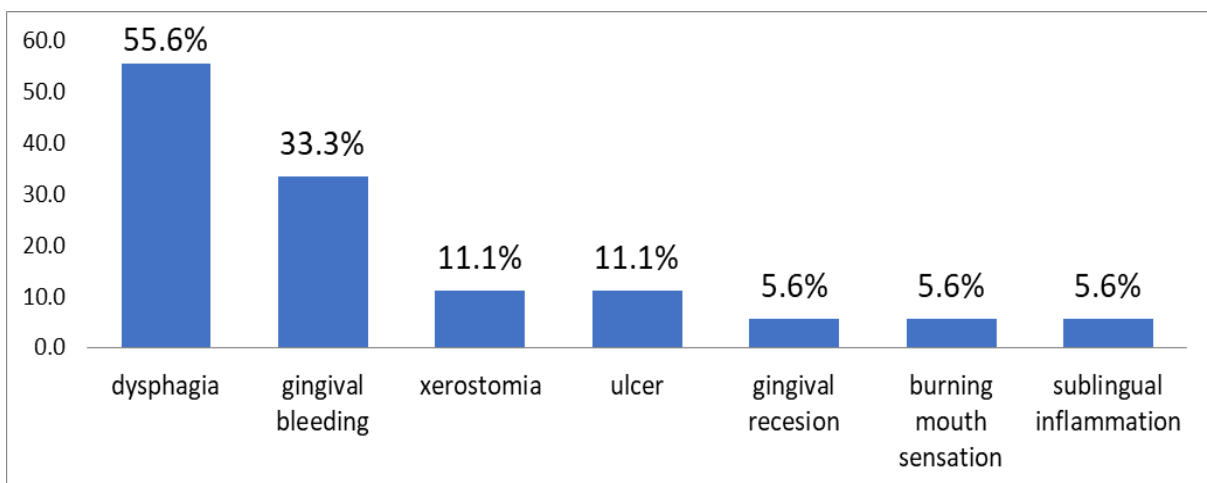
Figure 2: The percentage of oral side effects in patients using NSAIDs.

The most commonly used NSAIDs was Aspirin; which was used by 18 patients, and its oral side effects were gingival bleeding (no=14), xerostomia (no=10), taste disorders (no=8), ulcer (no=4) and gingival recession (no=1), as shown in the (Figure 3).



**Figure 3: The percentage of oral side effects in patients using aspirin.**

Another commonly used NSAID in this study was ibuprofen (no=18), and its oral side effects were dysphagia (no=10), gingival bleeding (no=6), xerostomia (no=2), ulcer (no=2), gingival recession (no=1), sublingual inflammation (no=1) and burning sensation (no=1), and their percentages are shown in (Figure 4).



**Fig4: The percentage of oral side effects in patients using ibuprofen.**

Mefenamic Acid was used by 16 patients and the oral side effects that accompanied its use were ulcerations (no=6) which were mostly of the aphthous type, other

seemingly common oral side effects were, xerostomia (no=4), taste disorders (no=4) and dysphagia (no=4) and other side effects. The percentages are shown in (Figure 5).

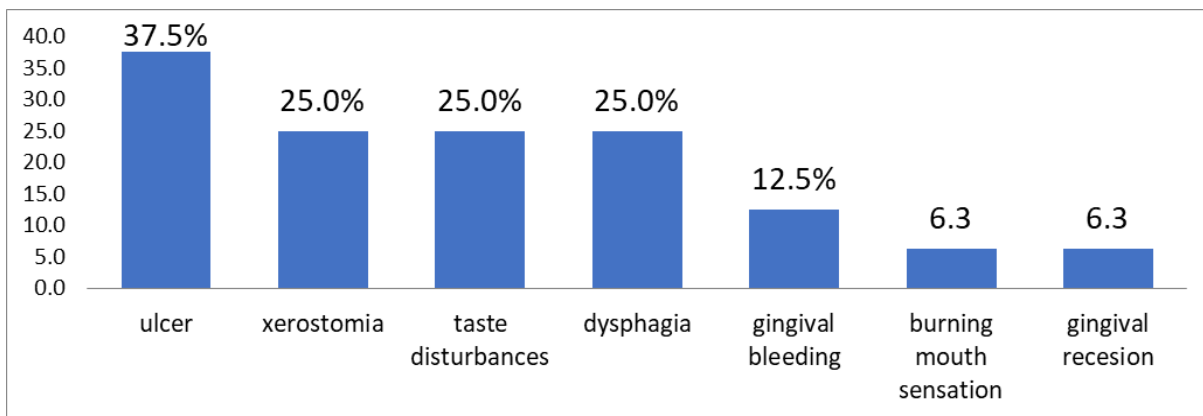


Figure 5: The most common oral side effects in patients using mefenamic acid.

The most commonly used drugs in patients using corticosteroids (no=20) were prednisolone (no=6), dexamethasone (no=4)

and Budesonide (no=4), triamcinolone (no=3) and hydrocortisone (no=3). The percentage of use are shown in (Figure 6).

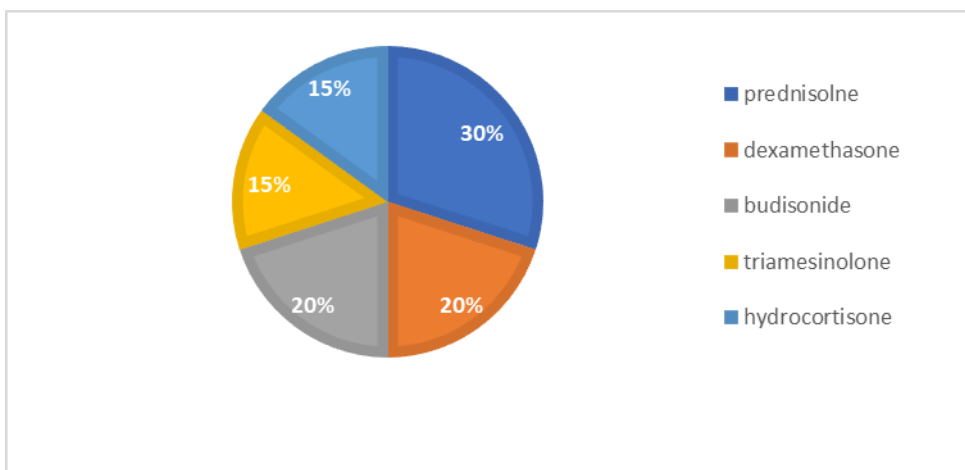


Figure 6: The percentages of drugs used in patients on corticosteroids.

The oral side effects that were presented among patients using corticosteroids were fungal infection (no=10), gingival inflammation (no=5), oral ulcer (no=2),

perioral dermatitis (no=3) and acne (no=1) and the percentage of use are shown in (Figure 7).

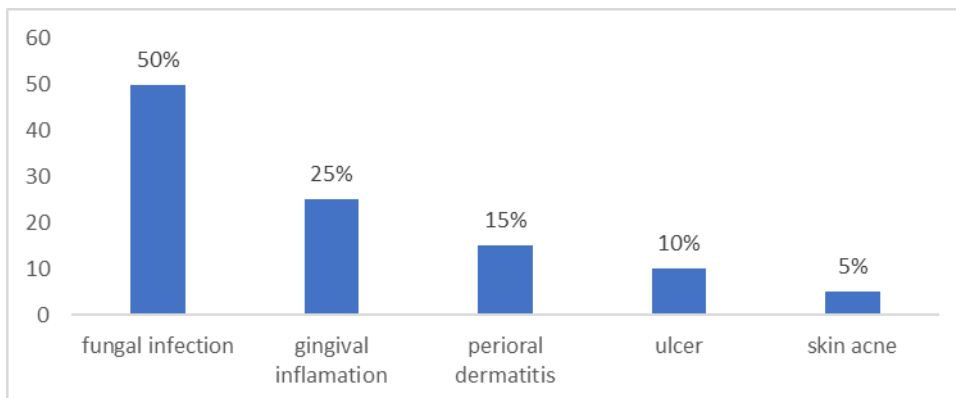
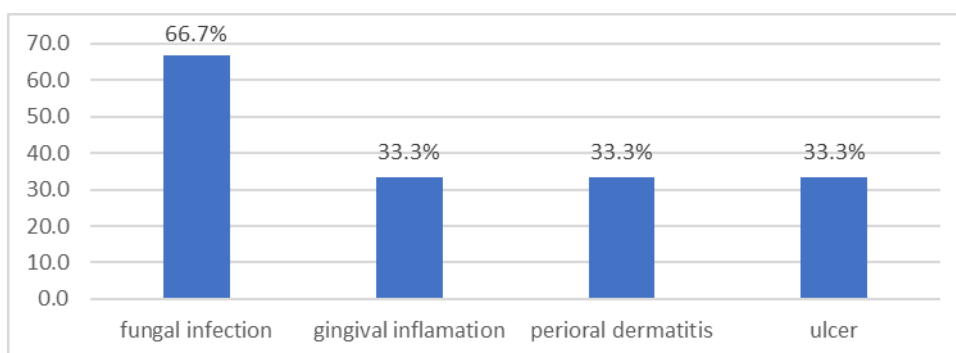


Figure 7: The oral side effects in patients using corticosteroids.

The oral side effects associated with the use of prednisolone were fungal Infection (no=4), gingival inflammation (no=2), ulcer (no=2) and perioral dermatitis (no=2). The percentages of these side effects are shown in (Figure 8).



**Figure 8: The oral side effects in patients using prednisolone.**

A statistical analysis was done to correlate the effect of age, gender, dose and the duration of using drugs with the manifestation of oral side effects for both

users of steroidal and NSAIDs using t-test, and p-value of  $\leq 0.05$  is considered significant. The results are shown in (Table 2 and 3).

**Table 2: Correlation of oral side effects in NSAIDs with gender, age, dose & duration.**

<i>Variable</i>	<i>Standard Error</i>	<i>t Stat</i>	<i>P-value</i>
NSAIDs - Gender	0.37429	2.3435	0.022*
NSAIDs - Age	0.17762	4.0921	0.000*
NSAIDs - Dose	0.00107	-1.8044	0.076
NSAIDs - Duration	0.40646	1.9880	0.061

\*significant at p value  $\leq 0.05$ .

**Table 3: Correlation of oral side effects in steroids with gender, age, dose & duration.**

<i>Variable</i>	<i>Standard Error</i>	<i>t Stat</i>	<i>P-value</i>
Steroids - Gender	0.60811	1.4783	0.156
Steroids - Age	0.31480	-0.6761	0.507
Steroids - Dose	0.0042	0.2923	0.773
Steroids - Duration	0.61370	1.5615	0.135

## DISCUSSION

Both steroidal and NSAIDs are the most commonly prescribed medications worldwide. This study showed that Aspirin, Ibuprofen and Mefenamic Acid were the most commonly used NSAIDs by the patients who enrolled in this study, the prevalence of Aspirin use seems to be mostly due to its anti-platelet effect that inhibits thromboxane A2 and inhibits thrombus formation which is mainly used for cardiovascular diseases rather than as an analgesic, as proven by taking medical history and this use has been confirmed by many clinical studies.<sup>23</sup> The prevalence of using Ibuprofen and mefenamic acid seemed to be directly proportional to their analgesic effect, as most of our cases taking these two drugs had a chief complaint of pain, this is further confirmed by many studies<sup>7,24</sup>, Ibuprofen and mefenamic acid are the most commonly used and most frequently prescribed NSAIDs for their prominent analgesic, anti-inflammatory and antipyretic action. While a study done by Varga et al in 2013 showed that ibuprofen is less frequently prescribed among hospitalized patients compared to other members of NSAIDs.<sup>25</sup>

The use of steroidal and NSAIDs is associated with many systemic adverse effects, and as dentists through our clinical practice we also may identify and correlate the side effects of using these drugs on the oral health. This study results concluded that gingival bleeding was the most common oral side effect associated with the use of NSAIDs (39%) however a majority of this side effect was attributed to the use of Aspirin itself, as (78%) of patients using Aspirin had gingival bleeding which is due to its irreversible anti-platelet action. A study done by Sundram et al in 2012 also showed a significant relationship between the use of aspirin and gingival bleeding and this is mainly due to its antiplatelet effect through inhibition of thromboxane A2-dependent platelet aggregation.<sup>26</sup> Other oral side effects of NSAIDs that has been identified in this study were xerostomia (32%) which in turn can cause other oral side effect as taste disturbances (29%) in addition to dysphagia (22 %) and this lies parallel with many previous studies that

linked other oral side effects to occur as a result of hyposalivation related to the use of NSAIDs and many other medications.<sup>27,28,1</sup> However Mefenamic acid was reported to induce hypersalivation.<sup>29</sup> Dysphagia, which was also a significant oral side effect of NSAIDs at (23%) prevalence, is an interesting finding; it mostly relates with the use of Ibuprofen, since we observed that (56%) of patients on an Ibuprofen prescription had complained of this symptom. The mechanism of this side effect could be the direct effect of xerostomia that complicate to dysphagia as a result of reduced saliva production and its lubricating effect in the oral cavity and throat<sup>27</sup>; and another mechanism revealed by a study done by Breslin et al 2011 found that ibuprofen – related dysphagia is due to its chemotactic properties causing direct irritation effect to the throat causing difficulty in swallowing.<sup>30</sup>

Ulcerations, particularly aphthous ulcers seemed to be another common oral side effect of NSAIDs representing (23%) and this side effect was mostly prevalent among Mefenamic acid users, which alone had a (38%) prevalence rate of ulcers.<sup>1</sup> Palla et al in 2022 also reported such an adverse effect related to the use of mefenamic acid 500mg for 3 days.<sup>31</sup> Although NSAIDs main mechanism for causing oral ulceration is by impairing the protective mucosa, it may also cause disturbances in nitric oxide generation and delay soft tissue repair.<sup>32</sup>

The differences in gender showed statistical significance ( $p$  0.02) in the occurrence of oral side effects related to the use of NSAIDs, as the cardinal side effects of gingival bleeding and gingival recession was most commonly presented in the female users of NSAID rather than in the males, while inversely, Xerostomia was more common in males than in females. There was statistically significant difference in the presentation of oral side effects between older and younger age ( $p$  0.00); this may be due to aging and delay in the repair of tissues and the multi-pharmacy among elderly.

Regarding corticosteroids, prednisolone was mostly used (30%), budesonide and dexamethasone (each represented 20%), and these drugs were mostly used for immune-



pathologies, including rheumatoid arthritis and allergies. budesonide was exclusively used by asthmatic patients.<sup>10,33</sup>

The most common oral side effect associated with the use of corticosteroids was fungal infections which was observed clinically as a white creamy thrush with a prevalence of (50%) of the other oral side effects, this is a commonly documented side effect of corticosteroids especially in chronic use and this is mainly due to immunosuppression.<sup>15,16</sup> This side effect appeared to be the most common in prednisolone (67%) users which is also confirmed by other studies.<sup>13,34,35</sup>

Inflammation of gingiva (25%) was also a significant oral side effects of the use Corticosteroids according to this survey. Similar to our findings a study done by Safkan et al in 1984 concluded that patients using corticosteroids are often predisposed to gingivitis.<sup>35</sup> Although corticosteroids have potential anti-inflammatory action but they can still enhance the deterioration of oral health.<sup>34</sup> Another oral side effect presented with the use of Corticosteroids was the oral ulcers (10%) which mostly occurred in patients using Prednisolone in combination with NSAIDs. Treatments with multiple drugs can exacerbate the occurrence of some oral side effects because both corticosteroids and NSAIDs can have a risk to cause ulcers as a part of their mechanism of action. A study done by Diaz and Rodreguez in 2001 found that the combination of steroids with NSAIDs can increase the risk of upper gastrointestinal ulcers.<sup>36</sup> Perioral dermatitis side effect was presented exclusively in old-age adults as scaly red rash around the mouth. The chronic use of corticosteroids especially the inhalers and topical dosage forms has been related to this side effect and a possible cause of this is an overgrowth of normal skin, mites and yeast.<sup>37</sup> There is a case report by Diehl and Cohen 2021 about 54 years old patient who developed perioral dermatitis due to applying high potency steroid topically.<sup>38</sup> However, denture use in elderly people is common and also could be a cause of perioral dermatitis but limited data was available regarding this drug induced oral side effects. The differences in gender, age, dose or duration did not show

any significant difference regarding the presentation of oral side effects associated with using corticosteroids.

## CONCLUSION

The use of steroidal and NSAIDs can have impact on the oral health and it is important to consider that drugs in general may cause oral side effects at different doses, dosage forms and durations of use and may have a variety of clinical oral manifestations. The dentists have crucial role in identifying these drug- related oral side effects through their clinical practices in order to provide the proper management for the patients.

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