

# Drug-induced Disorders of Teeth

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## ABSTRACT

It is essential that every health care professional who is involved with the prescription or recommendation of drugs be fully aware of any resultant disorders that may arise as a side-effect. A range of drugs can affect the teeth. In this review article, drugs that have the potential to induce changes in teeth have been classified as those leading to tooth discoloration (intrinsic and extrinsic), physical damage to tooth structure (enamel, dentin, and cementum), and alteration in tooth sensitivity.

**KEY WORDS:** oral, drugs, adverse reactions, teeth.

## INTRODUCTION

A range of drugs can affect the teeth (Billings *et al.*, 2004). Drugs that have the potential to induce changes in teeth can be classified as those leading to:

- tooth discoloration (intrinsic and extrinsic),
- physical damage to tooth structure (enamel, dentin, and cementum); and
- alteration in tooth sensitivity.

Drugs that affect other oral tissues have been discussed previously (Scully and Bagan, 2004).

### (1) DRUG-RELATED TOOTH DISCOLORATION

Numerous drugs are noted to have the capability to produce tooth discoloration, and this can either be extrinsic or intrinsic.

#### (a) Drug-related Extrinsic Tooth Discoloration

Extrinsic discoloration occurs after the tooth has erupted into the mouth. The drug subsequently causes superficial discoloration (Fig. 1) which can be removed by toothbrushing or professional cleaning. There have even been attempts to increase superficial discoloration to test the efficacy of dentifrices (Pontefract *et al.*, 2004).

Drugs that are well-recognized as causing extrinsic discoloration include chlorhexidine (Jensen, 1977, 1978; Addy *et al.*, 1979; Prayitno and Addy, 1979; Addy and Roberts, 1981), oral iron salts in liquid form (Dental Practitioners Formulary, 2004), essential oils (Moran *et al.*, 1991; Addy *et al.*, 1995) and co-amoxiclav (Garcia-Lopez *et al.*, 2001) (see Table 1).

From January, 1991, until June, 1995, 25 cases were reported to the Netherlands Pharmacovigilance Foundation (LAREB) of yellow to brown tooth discoloration following the oral use of liquid medication; 84% involved antibiotics, of which 14 were amoxicillin (Meyboom *et al.*, 1996). Since 1979, the Dutch Centre for Monitoring of Adverse Reactions to Drugs received 37 reports of tooth discoloration, attributed to the use of drugs, mostly to the use of amoxicillin and doxycycline or minocycline. Pseudo-discolorations are chiefly caused by antimicrobial agents, possibly by chromogenic precipitates in the pellicle, or by overgrowth with chromogenic micro-organisms (de Wit *et al.*, 1996). With the increasing frequency of methicillin-resistant *Staphylococcus aureus* in immunocompromised hosts, clinicians are increasingly prescribing the oral antimicrobial linezolid, an oxazolidinone. An immunocompromised 11-year-old girl with cellulitis was reported to develop superficial discoloration of her lower anterior teeth after receiving linezolid for 28 days (Matson and Miller, 2003).

#### (b) Drug-related Intrinsic Tooth Discoloration

Intrinsic tooth discoloration is permanent and occurs when the drug interferes with odontogenesis.

##### (i) Fluorides

Inorganic fluorides have long been recognized for their potential to reduce the magnitude and severity of dental decay in children



**Figure 1.** Extrinsic staining caused by a chlorhexidine mouthwash.



**Figure 2.** A typical presentation of dental fluorosis.

as well as adults (McClure, 1970; Klein, 1972). Although fluoride has substantial benefits in the prevention of tooth decay, depending on the level and source of exposure, fluorides also have adverse effects on human tissues (Hiller *et al.*, 1998).

Discoloration or damage to tooth structure may occur when the total daily intake of the fluoride ion from sources such as water, toothpaste, prescribed drops, and tablets is high while the enamel is undergoing pre-eruptive formation and maturation. The most common adverse effect of excess exposure to fluoride is dental fluorosis, a permanent hypomineralization of enamel, characterized in its mildest form as small, barely visible, white flecks found primarily on cusp tips and on facial surfaces of the permanent dentition (DenBesten, 1999). The moderate to severe forms are found on most permanent tooth surfaces and range between white opaque areas to darkly stained and pitted enamel (DenBesten, 1999) (see Fig. 2).

The critical window of exposure for fluorosis to manifest occurs during the early maturation stage of tooth development (DenBesten, 1999). Dental fluorosis is a dose-dependent condition, and the higher the level of exposure during tooth development, the more severe the fluorosis (Dean, 1942; Eklund *et al.*, 1987; Fejerskov *et al.*, 1990). In general, fluoride intake during critical periods of tooth development and maturation, from approximately birth to 8 years of age, is in the range of 0.03 to 0.1 mg F/kg body weight *per day* (Grobler *et al.*, 1986; Fejerskov *et al.*, 1987).

### (ii) Tetracyclines

In the early 1960's, clinical evidence began to appear suggesting that tetracycline could cause tooth discoloration (Olsen and Riley, 1966). This association was subsequently substantiated by several clinical and laboratory studies demonstrating that tetracycline becomes irreversibly bound to calcified tooth structures if it is administered during the calcification stage of tooth development (Guggenheimer, 1984). Tetracyclines are now well-recognized to result in the discoloration of tooth enamel when prescribed during tooth development.

Females exposed to tetracycline during the second or third

trimester of pregnancy may give birth to a child who will have discolored teeth. The teeth may become bright yellow upon development, and the stains will eventually turn to grey or brown over time (Driscoll *et al.*, 1993) (Fig. 3).

Since the majority of mineralization of the permanent dentition is not complete until a child is eight years of age (excluding third molars), tetracyclines should also not be used by anyone under that age. In pediatric patients who have received tetracyclines, one-third have reported tooth staining (www.Continuing Education.com, 2004). Discoloration occurs with the greatest frequency in the developing dentition when total dosage administration is over 3 g, or treatment exceeds 10 days (www.Continuing Education.com, 2004).

Depending on the specific tetracycline used, the type and severity of discoloration may vary (Driscoll *et al.*, 1993). Tetracycline and oxytetracycline cause a yellow discoloration, whereas chlortetracycline produces a grey-brown discoloration (Driscoll *et al.*, 1993). Evidence suggests that, of all the tetracyclines, oxytetracycline causes the least tooth discoloration (Wallman and Hilton, 1962). Tetracyclines (*e.g.*, Ledermix—triamcinolone acetonide and demethylchlortetracycline) used within the tooth for endodontic therapy may also cause dark grey-brown discoloration (Kim *et al.*, 2000). However, other anti-microbials, such as minocycline and ciprofloxacin, have also been reported to cause tooth discoloration (see Table 2).

### (iii) Minocycline

Minocycline is a semi-synthetic tetracycline derivative, first available in 1967 (Driscoll *et al.*, 1993), and is commonly used to treat acne vulgaris (Hubbell *et al.*, 1982) and rosacea

**Table 1.** Drugs Causing Extrinsic Tooth Discoloration

Drug	Discoloration Caused
Chlorhexidine	Yellow/brown
Oral iron salts	Black
Co-amoxiclav	Yellow or grey-brown
Essential oils	Yellow/brown



**Figure 3.** Tetracycline-induced intrinsic staining.

(Rebora, 2002). It is also used for the treatment of *Mycoplasma*, *Chlamydia*, and *Treponema* infections, chronic respiratory disease, rheumatoid arthritis (Tilley *et al.*, 1995), and as an adjunct in the management of periodontal disease (Seymour and Heasman, 1995). The use of minocycline in periodontal disease has seen a wide increase recently with the use of polymer beads as local carriers inserted directly into the periodontal pocket. Minocycline may cause abnormal pigmentation of the skin, thyroid gland, nails, bone, sclerae, and conjunctivae in adults. It has also been shown to cause tooth and bone discoloration in a few patients (Wolfe and Reichmeister, 1984; Cale *et al.*, 1988; Dodd *et al.*, 1998; Cheek and Heymann, 1999; McKenna *et al.*, 1999). Minocycline can stain teeth (Dodd *et al.*, 1998). Unlike tetracycline, minocycline has been reported to cause generalized intrinsic tooth staining post-eruption (Dodd *et al.*, 1998; Good and Hussey, 2003). This staining is distinctly different from that caused by tetracycline (see Table 3).

Staining of the adult dentition appears to occur in 3-6% of patients taking long-term minocycline at > 100 mg daily (Berger *et al.*, 1989; Westbury and Najera, 1997). The onset of discoloration can occur at any time from 1 month to many years after the initiation of treatment (Poliak *et al.*, 1985; Westbury and Najera, 1997).

The exact mechanism by which minocycline causes tooth discoloration is controversial and still under investigation. Currently, there are four possible theories: first, the 'extrinsic theory' (Berger *et al.*, 1989), where it is thought that minocycline attaches to the glycoproteins in acquired pellicles.

**Table 2.** Drug-related Intrinsic Tooth Discoloration

Drug-related Permanent Tooth Discoloration (intrinsic staining)	Discoloration Caused
Fluoride	White/brown discoloration
Tetracyclines	Yellow → brown/grey
Minocycline	Green-gray/blue-grey
Ciprofloxacin	Greenish

This in turn etches the enamel, and demineralization/rem mineralization cycles occur. It oxidizes on exposure to air or as a result of bacterial activity, and so causes degradation of the aromatic ring, forming insoluble black quinone. The second is the 'intrinsic theory' (Bowles and Bokmeyer, 1997; Bowles, 1998), where the minocycline bound to plasma proteins is deposited in collagen-rich tissues, such as teeth. This complex oxidizes slowly over time with exposure to light. This deposition in teeth occurs solely within the dentin matrix as secondary and reparative dentin is formed; the drug or its metabolic congeners do not affect enamel itself. The third possibility is that hemosiderin, a breakdown product of iron, chelates with minocycline to form an insoluble complex (Poliak *et al.*, 1985; Rosen and Hoffman, 1989). The fourth suggestion is that minocycline could be deposited in dentin during dentinogenesis (Good and Hussey, 2003).

#### (iv) Ciprofloxacin

Ciprofloxacin—a quinolone given intravenously to infants at dosages of 10 to 40 mg/kg/day to treat infections with *Klebsiella*—has been associated with greenish discoloration of the teeth when they erupted, and the discoloration could not be removed (Lumbiganon *et al.*, 1991).

## (2) DRUG-RELATED PHYSICAL DAMAGE TO TOOTH STRUCTURE

Some drugs have the potential to cause physical damage to tooth structure. Table 4 summarizes the categories of drugs and the subsequent possible damage that may result.

### (a) Medicines Containing Sugars

Any sugar-containing (liquid) medication has the potential to cause an increased incidence of dental caries (Mackie and Bentley, 1994). As such, it is essential that, wherever possible, practitioners and pharmacists should ensure the prescription of sugar-free medications, and advise parents to obtain sugar-free over-the-counter preparations.

**Table 3.** Comparison between Tetracycline- and Minocycline-stained Teeth (adapted from Good and Hussey, 2003)

	Tetracycline	Minocycline Hydrochloride
Color of staining	Yellow to brown/grey (Wallman and Hilton, 1962)	Green/grey, blue/grey (Poliak <i>et al.</i> , 1985; Rosen and Hoffman, 1989)
Pattern	Gingival margin or cervical third of crown (Wallman and Hilton, 1962) or band relating to duration and timing of drug administration	Incisal edge and, most intensely, the middle third of the crown (Poliak <i>et al.</i> , 1985; Rosen and Hoffman, 1989)
Severity	Severe	Less severe
Fluorescence	Yellow fluorescence	None clinically (Rosen and Hoffman, 1989) but will fluoresce in an acid medium
Resolution with drug stoppage	None	Resolution rare in teeth (Poliak <i>et al.</i> , 1985)

**(b) Tooth Erosion**

Tooth erosion may be caused by carbonated drinks and acidic fruits and their juices (Zero, 1996) and is commonly seen in individuals who use acidic "high energy" drinks during sports (Mathew *et al.*, 2002) and in wine tasters (Mok *et al.*, 2001).

Any drug that has the potential to cause gastro-esophageal reflux disease (GERD) can result in gastric acid reaching the oral cavity and a subsequent increased risk for tooth erosion. Examples of such drugs are listed in Table 4 (Bartlett and Smith, 1998).

Drugs such as aspirin (McCracken and O'Neal, 2000), and even some mouthwashes, may also cause erosion (Pontefract *et al.*, 2001; Pretty *et al.*, 2003).

Powdered versions of anti-asthmatic drugs—such as beclomethasone dipropionate, fluticasone, salmeterol, and terbutaline sulphate powders—have a pH lower than 5.5 and are more acidic than aerosol versions. Asthmatics who take such drugs in a powdered, rather than an aerosol, form are also at risk for tooth erosion (O'Sullivan and Curzon, 1998). This may be associated with increased GERD. Those taking these medications should thus rinse their mouths with water directly after taking the drugs and also be encouraged to clean their teeth thoroughly, at least twice a day, with a fluoride toothpaste.

**(c) Drugs That Result in Decreased Salivary Secretion**

Any drug that leads to decreased salivary secretion (dry mouth/xerostomia) can result in damage to teeth. As a result of decreased salivary secretion, the protective functions of saliva will be compromised, and this increases the susceptibility of the teeth to diseases such as dental caries. Dry mouth has a variety of possible drug causes (Scully, 2003; Scully and Bagan, 2004). The drugs that can result in dry mouth are illustrated in Table 5.

**(d) Drugs Used for Internal Tooth Bleaching**

Internal tooth bleaching can be used as an aesthetic treatment of non-vital discolored teeth. Both hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and sodium perborate (NaBO<sub>3</sub>) have been used, and various

**Table 4.** Drugs That May Lead to Damage to Tooth Structure

Drug	Examples	Possible Damage to Tooth Structure
Sugar-containing oral (liquid) medication	Various liquid medications	Dental caries
Drugs that result in decreased salivary secretion (xerostomia)	See Table 5.	Dental caries
Drugs with a pH low enough to cause tooth erosion	Aspirin, anti-asthmatic drugs	Dental erosion
Drugs that may increase susceptibility to gastro-esophageal reflux disease	Theophylline, anticholinergics, progesterone, calcium channel blockers, anti-asthmatics	Dental erosion
Drugs used for internal tooth bleaching	Hydrogen peroxide and sodium perborate	Cervical root resorption
Drugs used for treatment of childhood cancer and leukemia	Cytotoxic agents	Abnormal dental development
Anticonvulsants	Phenytoin	
Fluoride (see above)		Dental fluorosis

**Table 5.** Drugs Implicated in Xerostomia

Drugs Most Commonly Implicated	Drugs Occasionally Implicated
Alpha receptor antagonists	Amphetamines
Anticholinergics	Antihistamines
Antidepressants (serotonin agonists, or noradrenaline and/or serotonin re-uptake blockers)	Antihypertensive agents
Antipsychotics such as phenothiazines	Antimigraine agents
Atropinics	Appetite suppressants
Muscarinic receptor antagonists	Benzhexol
HIV protease inhibitors	Benzodiazepines, hypnotics, opioids
Radioiodine	Benzotropine
	Biperiden
	Bronchodilators
	Clonidine
	Cyclobenzaprine
	Cytokines
	Cytotoxics
	Dideoxyinosine
	Decongestants and 'cold cures'
	Diuretics
	Fenfluramine
	Fluoxetine
	Ganglion-blocking agents
	H2 antagonists/proton pump inhibitors
	Ipratropium
	Isotretinoin
	L-dopa
	Lithium
	Monoamine oxidase
	Omeprazole
	Opiates
	Orphenadrine
	Phenothiazines
	Propantheline
	Retinoids
	Selegiline
	Skeletal muscle relaxants
	Thiabendazole

**Table 6.** Studies to Support Correlation between Internal Tooth Bleaching and Cervical Root Resorption

Internal Bleaching Procedure	Type of Study	Observation Time	No. of Patients	No. of Teeth	Trauma	Cervical Resorption	Reference
H <sub>2</sub> O <sub>2</sub> (a)	Case report			2	2	All teeth	Latcham, 1986, 1991
NaBO <sub>3</sub> + 30% H <sub>2</sub> O <sub>2</sub>	Case report			1	1	All teeth	Goon <i>et al.</i> , 1986
NaBO <sub>3</sub> + 30% H <sub>2</sub> O <sub>2</sub> + Heat (b)	Case report			18	15	All teeth	Harrington and Natkin (1979); Lado <i>et al.</i> (1983); Cvek and Lindvall (1985); Gimlin and Schindler (1990); Al-Nazhan (1991)
NaBO <sub>3</sub> + 30% H <sub>2</sub> O <sub>2</sub> (replaced once a week)	Follow-up	3-15 years	20	112	No	0%	Abou-Rass (1998)
NaBO <sub>3</sub> + oxygen-water	Follow-up	4 years	31	248	No	0%	Anitua <i>et al.</i> (1990)
NaBO <sub>3</sub> , replaced every 10-15 days	Follow-up	3 years	86	95	96%	0%	Holmstrup <i>et al.</i> (1988)
(a) + (b)	Follow-up	1-8 years	46	58	38%	6.9%	Friedman <i>et al.</i> (1988)

heat sources have been applied to accelerate the reaction and improve the bleaching effect (Howell, 1980). An adverse effect that has been reported following internal tooth bleaching is cervical root resorption (an inflammatory-mediated external resorption of the root) (Friedman *et al.*, 1988). Dahl and Pallesen (2003) reviewed the published case reports on cervical root resorption following intracoronal bleaching. Table 6 summarizes the available data to support a correlation between internal tooth bleaching and cervical root resorption.

A high concentration of hydrogen peroxide in combination with heating seems to promote cervical root resorption (Friedman *et al.*, 1988; Baratieri *et al.*, 1995). Thus, it appears that the use of a thermo-catalytic bleaching procedure in teeth with cervical defects of the cementum constitutes a risk factor for the development of cervical resorption. It should also be noted that intracoronal bleaching with 30% hydrogen peroxide has been found to reduce the micro-hardness of dentin and enamel (Lewinstein *et al.*, 1994) and weaken the mechanical properties of the dentin (Chng *et al.*, 2002).

### (e) Anticonvulsants

There have been several reports of the effects on dental development of pre- and post-natal administration of

anticonvulsants (Robinson *et al.*, 1983; Orup *et al.*, 1998).

Pre-natal exposure to anticonvulsants has been shown to cause craniofacial dysmorphism, pre-natal growth retardation, hypoplastic nails and phalanges, and visceral abnormalities, as well as a significant increase in mesiodistal crown dimensions of the posterior maxillary teeth—specifically, primary molars and their permanent premolar successors, as well as permanent molars. Changes in tooth size were more common in females than in males. Dental maturity, assessed with the use of panoramic radiographs, was equal to chronological age. An increased frequency of hypodontia was the only clinically notable dental anomaly (Orup *et al.*, 1998), but root formation can be disturbed (Robinson *et al.*, 1983)—an effect demonstrable in animal models (Robinson *et al.*, 1978).

### (f) Chemotherapeutic Drugs

Studies on drugs used for the treatment of childhood cancer and leukemia have consistently shown that children younger than 5 years at diagnosis and the start of treatment exhibit abnormal dental development (Dahllöf *et al.*, 1994). The severity of dentofacial-developmental and tooth-related abnormalities secondary to the therapy are related to the age of the child, the dosage, and the duration of treatment (Dahllöf *et al.*, 1994).

Dental abnormalities include tooth agenesis, arrested tooth development, microdontia, and disturbances affecting enamel, dentin, and cementum (Jaffe *et al.*, 1984; Durr *et al.*, 1987; Rosenberg *et al.*, 1987; Pajari *et al.*, 1988; Nunn *et al.*, 1991; Kaste *et al.*, 1997; Alpaslan *et al.*, 1999).

### (3) DRUG-RELATED ALTERATION TO TOOTH SENSITIVITY

External tooth bleaching has been conducted with the use of hydrogen peroxide or carbamide peroxide (which releases hydrogen peroxide) and can take place at home or in the dental surgery. Tooth

**Table 7.** Studies to Support Correlation between External Tooth Bleaching and Cervical Sensitivity

Type of Treatment	Bleaching Procedure	Duration of Study	No. of Patients	No. of Controls	Incidence of Sensitivity	Reference
In-surgery	30% H <sub>2</sub> O <sub>2</sub> + heat, 30 visits of 30 min during 3 wks	30 days	19	0	78%	Cohen and Chase, 1979
In-surgery	30% H <sub>2</sub> O <sub>2</sub> + heat, 2-6 visits of 30 min	No data given	15	0	67%	Nathanson and Parra, 1987
At-home	10% carbamide peroxide, 2 hrs or overnight	28 days	28	0	15%	Schulte <i>et al.</i> , 1994
At-home	10% carbamide peroxide overnight	14 days	24	0	64%	Tam, 1999a
At-home	10% carbamide peroxide, day or night	6 wks	37	0	38%	Leonard <i>et al.</i> , 1997
At-home	10% carbamide peroxide, 6-8 hrs/day + solution changes	6 wks	38	0	52%	Leonard <i>et al.</i> , 1997
At-home	10% carbamide peroxide, day + night or day w/solution changes	6 wks	27	0	78%	Leonard <i>et al.</i> , 1997

sensitivity is a common adverse effect of external tooth bleaching (Table 7) (Tam, 1999b).

Data from various studies where 10% carbamide peroxide was used indicate that from 15 to 65% of the patients reported increased tooth sensitivity (Haywood *et al.*, 1994; Schulte *et al.*, 1994; Leonard *et al.*, 1997; Tam, 1999a). Higher incidences of tooth sensitivity (from 67 to 78%) were reported after in-surgery bleaching with hydrogen peroxide in combination with heat (Cohen and Chase, 1979; Nathanson and Parra, 1987). Tooth sensitivity normally persists for up to 4 days after the cessation of bleaching treatment (Cohen and Chase, 1979; Schulte *et al.*, 1994), but a longer duration of up to 39 days has been reported (Leonard *et al.*, 1997; Tam, 1999a). The mechanisms that account for tooth sensitivity after external tooth bleaching have not yet been fully established.

This review article has illustrated that many drugs can have an adverse effect on teeth. It is important that any individual involved with the prescription of these drugs comprehensively understand any potential side-effects that they may have and that, with this knowledge, the individual prescribes them having carefully considered the benefits *vs.* adverse effects that may occur as a result.

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