Dental Treatment of Patients with Mental Disorders

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Faculty Disclosure
Contributing faculty, Mark J. Szarejko, DDS, FAGD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Audience
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Course Objective

In dentistry, mental health disorders are commonly encountered in patients and can impact oral health and the level of care that can be provided. The purpose of this course is to provide dental professionals with the information necessary to identify mental health disorders and to address these issues appropriately.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the most frequently diagnosed mood disorders and potential impact on oral health.

2. Identify anxiety disorders and considerations for anxiety during dental treatment.

3. Discuss the presentation of post-traumatic stress disorder (PTSD) and impact on dental care.

4. Review considerations for dental patients with schizophrenia.

5. Analyze necessary modifications to dental treatment to accommodate the needs of patients with somatoform disorders.

6. Describe alterations in oral health that may arise from substance use disorders or medications used in their treatment.

E B
EVIDENCE-BASED
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RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Providing optimum treatment to dental patients requires a comprehensive understanding of the entire spectrum of their medical history. Systemic illnesses, including mental illnesses, can have a direct impact on oral health or an indirect impact via medications used in treatment. It is unfortunate that a stigma still exists about mental illness, as these are medical conditions that require appropriate assessment and management. It is this stigma that prevents many patients from seeking treatment, which can promote positive change and a higher quality of life.

Mental disorders are diagnosed or systemic conditions that can alter thought, mood, or behavior (individually or collectively) and that cause distress and impair function [1]. It is estimated that 25% of adults in the United States currently have a mental illness and that 50% of adults in the United States will experience at least one mental illness during their lifetime [2]. This represents a large portion of the U.S. population, many of whom will seek dental care.

This course will serve as an introduction to the most common mental illnesses in the United States, including description of the most prevalent symptoms of each. Further, potentially adverse oral and dental effects of mental disorders and/or treatments will be explored. A review of dental treatment modifications that may be required will be provided. Although this course focuses on a selected group of mental disorders, it should provide insight into the general needs of these patients and the necessity for considering mental health in all dental patients.

MOOD DISORDERS

BIPOLAR DISORDER

Bipolar disorder, also known as manic depressive disorder, is a mood disorder that affects 1% to 2% of the adult population, without a statistically significant difference of occurrence between men and women [3]. Bipolar disorder I features alternation of major depressive episodes with full manic episodes; bipolar disorder II is characterized by major depressive episodes and manic episodes that are less severe than those seen in bipolar I disorder [4]. A manic episode is defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) with the following criteria [5]:

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary)

- During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree and represent a noticeable change from usual behavior:
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep
  - More talkative than usual or pressure to keep talking (pressured speech)
  - Flight of ideas or subjective experience that thoughts are racing
  - Increase in goal-directed activity or psychomotor agitation
  - Excessive involvement in pleasurable or hedonistic activities with a high potential for painful consequences

- The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features

- The episode is not attributable to the physiologic effects of a substance (e.g., an illicit drug, a medication, other treatment) or to another medical condition

At least one lifetime manic episode is required for the diagnosis of bipolar I disorder [5; 6]. The elation and euphoria of this phase can be of such a magnitude that the patient may feel that he/she is cured of bipolar disorder and may discontinue the use of their medication(s).

Common characteristics of the depressive phase include lethargy, prolonged sadness, decreased self-esteem, contemplation of death or suicide, problems with concentration and memory, insomnia, loss of interest in activities that were previously enjoyable, and loss of appetite [7].

The duration of time in between episodes and the actual time in a manic or depressive phase varies considerably among patients. Some patients cycle between mania and depression several times during the course of a day or a week, while other patients may experience bipolar episodes only a few times each year. Other patients may remain in either the manic or the depressive phase for weeks or months at a time [8]. Patients who experience bipolar episodes at least four times per year are known as "rapid cyclers." These patients are more resistant to conventional medical treatment [9].

The initial diagnosis of bipolar disorder is usually made during adolescence or early adulthood, when the patient exhibits a first manic episode. This may precede a depressive episode.

The underlying etiology of bipolar disorder is not completely understood. A genetic predisposition is hypothesized to play a role, as studies with monozygotic (identical) twins yield concordance rates of 60% to 80% while the rates decline to 14% to 23% for dizygotic (fraternal) twins [10]. Other researchers have suggested that problems with mitochondrial energy production may contribute to the development of the disorder [11].

Medical Treatment

There is no current cure for bipolar disorder, and long-term treatment is designed to allow for better control of manic/depressive swings. Treatment plans generally consist of pharmacotherapy, psychotherapy, and lifestyle modification that can be encouraged with family and peer support.

Mood stabilizers have long been the first choice for the pharmacologic management of bipolar disorder. Among these medications, lithium is most frequently prescribed. This agent helps to prevent manic episodes and to decrease the risk of suicidal behavior [12]. However, it is not always effective and its side effects can preclude its use.

The long-term use of lithium can cause adverse cardiovascular, central nervous, endocrine, hematologic, and neuromuscular effects [13]. In oral health, perhaps the most significant adverse effect of long-term lithium use is xerostomia (dry mouth). Interventions for xerostomia (dry mouth) include artificial saliva substitutes, frequent sips of water, or cholinergic medications, such as pilocarpine. Immunoglobulins and other compounds present in saliva that support immune functions will have a decreased output and can subject patients to recurring opportunistic infections, such as oral candidiasis. Impaired salivary flow will also cause a decrease in saliva's cleansing action upon the teeth. Further, the ability of salivary components to maintain the pH of saliva as a mild base is altered, which causes the oral environment to become more acidic.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) such ibuprofen and naproxen to manage dental or oral pain is common, but these medications can decrease the renal clearance of lithium and increase its serum concentration to toxic levels. As such, concurrent use of NSAIDs and lithium should be avoided in favor of acetaminophen-based analgesics, if appropriate. Patients taking lithium should also be cautioned to avoid over-the-counter NSAIDs.

The antibiotic metronidazole is occasionally used as a single agent or in conjunction with beta-lactam antibiotics (e.g., amoxicillin) to treat odontogenic infections. Metronidazole can also decrease the renal clearance of lithium and cause subsequent elevation in its plasma concentration, increasing the risk for lithium toxicity. As such, an antibiotic that is compatible with the patient's medical history should be used instead.

If lithium is ineffective or causes unacceptable side effects, valproic acid or carbamazepine may be used as a second-line option for patients with bipolar disorder. Valproic acid can potentiate central nervous system (CNS) depression seen with opioid analgesics and benzodiazepines (e.g., diazepam). Carbamazepine can decrease plasma concentrations of acetaminophen and tramadol and decrease their analgesic efficacy [14].

Macrolide antibiotics (e.g., erythromycin, azithromycin, clarithromycin) can increase the plasma concentration of valproic acid and carbamazepine, which can lead to systemic toxicity [15]. Alternative effective antibiotics should be used. Any other prescribed or over-the-counter medications that are used by the patient should be evaluated for potential adverse drug interactions with those used adjunctive to dental treatment.

Dental Treatment Modifications

As with any patient, dental treatment of a patient with bipolar disorder begins with a thorough review of the patient's current state and medical history. Patients experiencing a manic episode may display signs of hyperactivity, including grinding of teeth and excessive frequency and application of force during tooth brushing, which can lead to cervical abrasion and trauma to the gingival tissues. The subsequent sensitivity from the exposed dentin can discourage the patient from proper oral hygiene practices and increase the risk of caries and periodontal disease. Dental staff should provide the patient with a mirror view of any area of cervical abrasion and provide individualized oral hygiene instructions to maintain optimal oral hygiene without perpetuating the cycle of abrasion.

Patients experiencing a depressive episode may disregard oral hygiene. If this phase is extensive and oral hygiene is neglected for an extended period, caries and periodontal disease may develop or worsen. Patients with partial or complete dentures may neglect daily maintenance, with a consequent accumulation of food debris and micro-organisms that can cause inflammation of the underlying tissues and preclude the ability to wear the prostheses.

If possible, dental appointments should be scheduled between bipolar episodes, as patients who are in a manic or depressive phase may have difficulty enduring dental appointments or comprehending complex treatment plans, financial arrangements, and/or issues related to informed consent. The patient's physician should be contacted before initiation of treatment if there is any concern about the patient's ability to endure the proposed dental treatment plan.

MAJOR DEPRESSIVE DISORDER

Depressive disorders afflict approximately 17.3 million Americans each year [16; 17; 18]. MDD affects approximately 22.2 million American adults, or about 7% of the U.S. population 18 years of age and older in a given year. The lifetime incidence of depression in the United States is 20% in women and 13% in men, or about 17% of all Americans. Depression is more common in persons with medical illnesses, with 11% to 36% of general medical inpatients fulfilling diagnostic criteria for MDD [5; 19; 20; 21]. The DSM-5 umbrella of depressive disorders includes MDD (including major depressive episode), persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, unspecified depressive disorder, and disruptive mood dysregulation disorder, a new diagnosis added to address concerns about the potential overdiagnosis of and treatment for bipolar disorder in children up to 12 years of age [5]. Of these types, MDD is the most common type.

To meet the diagnosis of MDD, a person must have at least five of the following symptoms for at least two weeks' duration and represent a change from previous functioning. At least one of the symptoms must be either depressed mood or loss of interest or pleasure [5]:

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all or almost all activities most of the day or nearly every day
- Significant weight loss or gain (>5% body weight) or increase or decrease in appetite
- Insomnia/hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue/loss of energy nearly every day
- Feelings of worthlessness or inappropriate guilt nearly every day
- Diminished concentration or indecisiveness nearly every day
- Recurrent thoughts of death or suicide, suicide attempt, or a specific plan for committing suicide

In addition, the symptoms must not meet the criteria for a mixed episode. The patient with MDD has never experienced a manic, mixed, or hypomanic episode. Symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Additionally, the symptoms may not be due to the direct physiologic effects of a recreational or prescribed drug or be better accounted for by bereavement (i.e., after the loss of a loved one, the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation) [5].

The diagnostic symptoms of MDD represent the domains of affective, behavioral, cognitive, and somatic impairment. Affective or mood symptoms include depressed mood and feelings of worthlessness or guilt, while behavioral symptoms include social withdrawal and agitation. Cognitive symptoms include difficulties with concentration or decision making, and somatic or physical symptoms include insomnia or fatigue.

The DSM-5 diagnostic criteria for MDD also include several specifiers to further describe the nature of the current episode of MDD. These specifiers include [5]:

- Anxious distress
- Mixed features
- Melancholic features
- Atypical features
- Mood-congruent psychotic features
- Mood-incongruent psychotic features
- Catatonic features
- Peripartum onset
- Seasonal pattern

Pharmacotherapy

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have advantages of low overdose lethality and better tolerability than first-generation antidepressants, which can improve adherence. SSRIs are particularly effective in patients with obsessive-compulsive symptoms, but may initially worsen anxiety or panic symptoms [17; 22; 23]. This class includes the agents fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), escitalopram (Lexapro), and vortioxetine (Brintellix). Citalopram may have fewer drug-drug interactions than other SSRIs, and fluoxetine may be a better choice in patients with poorer adherence due to its long half-life [17; 22; 23].

The most common side effects with SSRIs are gastrointestinal (nausea, vomiting, and diarrhea), activation/insomnia (restlessness, agitation, anxiety, akathisia, and sleep disturbances), sexual, headache, fatigue, and weight gain [17; 22; 23]. Xerostomia can also occur with the use of SSRIs. Many of these side effects dissipate over time.

Platelet aggregation can be impaired due to platelet serotonin depletion, which can interfere with the ability to achieve hemostasis during oral or periodontal surgery or root planing and curettage procedures. The concurrent use of NSAIDs or daily aspirin as a cardioprotective measure can exacerbate this problem and should be avoided, particularly if invasive dental procedures are planned. SSRI-induced bruxism (the involuntary grinding or clenching of the teeth) has been reported [13]. For patients prescribed SSRIs who have dental phobia or anxiety, anxiolytic medications should be only be given following consultation with the patient's physician, as this combination can potentiate CNS depression and increase the risk for respiratory arrest.

If an SSRI or tricyclic antidepressant (TCA) is combined with tramadol (an analgesic used for moderate-to-severe pain), serotonin syndrome may develop. Mild cases of serotonin syndrome present with signs and symptoms such as anxiety, diaphoresis, and gastrointestinal complaints. Severe cases can present with confusion, hypertension, hyperthermia, hyper-reflexia, and seizures [24]. The serotonin toxidrome has a variable presentation and can be difficult to detect. The most distinguishing features are clonus, fever, and hyper-reflexia, but the most important diagnostic clue is a history of exposure to serotonergic drugs. Given the potentially serious and even deadly effects of combining these medications, tramadol should be avoided and another analgesic chosen for these patients.

SSRIs have also been associated with alteration in taste (dysgeusia), sialadenitis (inflammation of the salivary glands), stomatitis (inflammation of the mucosal lining of any of the structures of the mouth), and edema of the tongue [25]. Patients who experience dysgeusia may use extra salt or sugar to compensate for the decreased ability to taste. These compensatory mechanisms are contrary to good general and oral health. The pain associated with stomatitis can discourage patients from maintaining optimal oral hygiene.

While these adverse oral effects will resolve upon cessation of SSRI use, halting the medication suddenly is dangerous. Titration or switching to another class of antidepressant should only be attempted by the patient's physician.

Serotonin-Norepinephrine Reuptake Inhibitors

Most serotonin-norepinephrine reuptake inhibitors (SNRIs), including venlafaxine (Effexor), desvenlafaxine (Pristiq), levomilnacipran (Fetzima), and duloxetine (Cymbalta), are several-fold more selective for serotonin than norepinephrine. Safety, tolerability, and side effect profiles of SNRIs resemble SSRIs, with the exception that the SNRIs have been associated (rarely) with sustained elevated blood pressure [17; 22; 23]. As such, patients taking SNRIs are at risk for xerostomia, bruxism, and drug-drug interactions.

Tricyclic Antidepressants

TCAs are predominantly serotonin and/or norepinephrine reuptake inhibitors that act by blocking the serotonin transporter and the norepinephrine transporter, respectively, which results in an elevation of the extracellular concentrations of these neurotransmitters, and therefore an enhancement of neurotransmission. TCAs also have varying but typically high affinity for the H1 and H2 histamine receptors and muscarinic acetylcholine receptors. As a result, they also act as potent antihistamines and anticholinergics. These properties are generally undesirable in antidepressants, however, and likely contribute to their large side effect profiles [26].

TCAs are comparable in efficacy to SSRIs/SNRIs, but their side effect profile makes them seldom used as first-line therapy [17; 22; 23]. TCAs may initially worsen anxiety or panic symptoms. Due to side effect potential of cardiac arrhythmia, TCAs should be used very cautiously, if at all, in patients with heart problems. Issues with orthostatic hypotension and sedation, particularly in elderly patients, also arise and may be a concern following dental appointments.

Anticholinergic and antihistamine activity accounts for many side effects, including xerostomia, blurred vision, reduced gastrointestinal motility or constipation, urinary retention, cognitive and/or memory impairment, and increased body temperature [17; 22; 23]. Other side effects may include drowsiness, anxiety, emotional blunting (apathy/anhedonia), confusion, restlessness, dizziness, akathisia, hypotension, tachycardia, and arrhythmia. As with SSRIs, patients taking TCAs may develop dysgeusia, sialadenitis, stomatitis, and lingual edema. Tolerance to side effects often occurs if treatment is continued. Side effects may also be less troublesome if treatment is initiated with low doses and gradually increased [26; 27].

The prolonged use of TCAs can cause suppression of the production of the formed elements of human blood, and this decreased production of platelets can result in coagulation problems after invasive dental procedures [14]. Similarly, decreased production of granular and agranular leukocytes can lead to an increased potential for opportunistic oral infections and delayed healing of intraoral surgical sites. A complete blood count (CBC) with differential and adjunctive laboratory tests (e.g., prothrombin time [PT], partial thromboplastin time [PTT]) are advisable prior to any dental procedure in which the ability to achieve hemostasis is required.

TCAs may also accentuate the effects of vasoconstrictors in local anesthetic solutions (e.g., epinephrine, levonordefrin), which can culminate in a rare but serious hypertensive crisis. This potential adverse effect is more pronounced when a TCA is combined with levonordefrin [28]. If appropriate, a local anesthetic solution without a vasoconstrictor (e.g., mepivacaine, prilocaine) should be used for these patients, keeping in mind that the duration and depth of anesthesia will be reduced. If a local anesthetic with a vasoconstrictor is used in a patient also taking a TCA, a cautious and conservative approach is mandatory.

Suicide

Among persons with a mood disorder, 12% to 20% will ultimately die by suicide. The first three months after diagnosis is the period of highest risk for a first attempt, with the three months following the first attempt being the highest risk period for a second attempt [154].

Most people who are suicidal exhibit warning signs, whether or not they are in an acute suicide crisis. These warning signs should be taken seriously and include observable signs of serious depression; withdrawal from friends and/or social activities; sleep problems; and loss of interest in personal appearance, hobbies, work, and/or school [155]. Although dental professionals may feel uncomfortable with suicidal patients, it is essential not to ignore or deny the suspicion of suicide risk. The first and most immediate step is to allocate adequate time to the patient, even though many others may be scheduled, in order to show empathy and build rapport. Patients at risk for suicide should be referred to a behavioral health provider. If suicide is an imminent risk, contacting emergency medical services may be warranted.

Dental Treatment Modifications

As discussed, the oral health of patients with major depressive disorder can be compromised by the direct and indirect effects of the medications that are used in its treatment and by the manner in which this disorder affects the patient's motivation to maintain optimal oral hygiene and attend periodic dental recall appointments. However, there are no universal modifications that apply to the dental treatment for these patients. Motivation of the patient to maintain optimal oral hygiene at home and to continue attendance at periodic recall appointments is a challenge, although this is an issue for many patients without depression as well. The length of a dental appointment should reflect the patient's ability to withstand dental treatment. Longer appointments and more complex dental procedures should only be scheduled if necessary. If there is any doubt about the degree to which major depressive disorder affects a patient's ability to commit to a treatment plan, withstand dental treatment, or tolerate medications, consultation with the patient's physician or psychiatrist is recommended.

ANXIETY DISORDERS

Anxiety disorders are characterized by states of chronic, excessive dread or fear of everyday situations. The fear and avoidance can be life-impairing and disabling. Anxiety disorders result from the interaction of biopsychosocial factors, whereby genetic vulnerability interacts with situations, stress, or trauma to produce clinically significant syndromes. The influence of hereditary factors and adverse psychosocial experiences on pathogenesis and pathophysiology is complex, but neuroscience advances have greatly improved the understanding of the underlying factors in the development and maintenance of anxiety disorders. Each year in the United States, anxiety disorders impact approximately 42 million adults [29; 30].

While there are many disorders under the umbrella of anxiety disorders, the conditions with the most impact on dental care are generalized anxiety, panic disorder, and specific phobia.

GENERALIZED ANXIETY DISORDER

Studies in the United States on generalized anxiety disorder prevalence rates have found a 5.1% lifetime rate and a 2.0% to 3.1% past-year rate. The lifetime and past-year prevalences are 3.6% and 2.0% in men/boys and 6.6% and 4.3% in women/girls. The majority of persons with generalized anxiety disorder diagnoses are female. Childhood or adolescent onset was found in more than 50% of those seeking help for anxiety, reflecting the chronicity of the disease [5].

Generalized anxiety disorder is characterized by excessive and inappropriate worrying that is persistent and not restricted to particular circumstances. Patients have physical anxiety symptoms and key psychologic symptoms. Generalized anxiety disorder is often comorbid with major depressive disorder, panic disorder, phobia, health anxiety, and obsessive-compulsive disorder [31]. The diagnostic criteria for generalized anxiety disorder are [5; 32]:

- Excessive anxiety and worry (apprehensive expectation) over a number of everyday concerns (e.g., school/work performance)
- Individual finds it difficult to control the worry
- Excessive anxiety and worry are associated with three or more of the following six symptoms, with at least some occurring more days than not for at least six months:
  - Restlessness, feeling "on edge"
  - Easily fatigued
  - Difficulty concentrating
  - Irritability
  - Muscle tension
  - Sleep disturbance (difficulty falling or staying asleep, restless sleep)
- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- Symptoms not better explained by another mental disorder
- The disturbance is not attributable to the physiologic effects of a substance or another medical condition

Medical Treatment

The primary goals of generalized anxiety disorder treatment are reduction of anxiety symptoms and reduction or elimination of disability. Pharmacotherapy and CBT or cognitive therapy are equal as first-line options.

The Anxiety Disorders Association of Canada and the Anxiety and Depression Association of America have created guidelines for the selection of appropriate pharmacotherapy in the treatment of generalized anxiety disorder with differing recommendations regarding first- and second-line medications [33; 34]. The Anxiety Disorders Association of Canada recommends agomelatine, pregabalin, venlafaxine XR, duloxetine, escitalopram, paroxetine, or sertraline as first-line options, while the Anxiety and Depression Association of America suggests venlafaxine XR, duloxetine, paroxetine, escitalopram, sertraline, or fluoxetine [33; 34].

Oral Health Implications and Dental Treatment Modifications

As discussed, depression of the respiratory system and the CNS can occur with the use of benzodiazepines, especially in conjunction with alcohol or opioid analgesics. Dental clinicians should use non-opioid analgesics to treat pain if a patient is being treated with a benzodiazepine. Some dental practices use benzodiazepines to help calm apprehensive patients so they may receive treatment (marketed as "sleep dentistry"). Patients who are already taking a benzodiazepine to treat generalized anxiety disorder should not take an additional dose of any other benzodiazepine medication as an anxiolytic before dental treatment, as this combination can also potentiate respiratory and CNS depression.

Macrolide antibiotics (e.g., erythromycin, clarithromycin, azithromycin) used to treat odontogenic infections can increase blood plasma levels of alprazolam, with the potential for systemic toxicity. So, the simultaneous use of these medications is contraindicated [14]. Instead, alternative antibiotics (e.g., penicillin, amoxicillin, clindamycin) compatible with the patient's medical history should be used.

The pharmacokinetics of benzodiazepines should also be considered when medications are used adjunctive to dental treatment. Specifically, the half-life (i.e., the interval of time required to achieve a 50% reduction in blood plasma concentration) of benzodiazepines can be affected by drug interactions. An extended half-life results in a lingering drug effect.

Diazepam (via its active metabolite desmethyldiazepam) has a half-life that can range from 50 to 100 hours, compared with 40 hours for lorazepam and 11.2 hours for alprazolam [35]. Thus, the adverse interactions between diazepam and opioids can occur for approximately four days after the last dose of diazepam is taken. Although the half-lives of lorazepam and alprazolam are considerably less than that of diazepam, precaution for the expected half-lives of those drugs is also recommended.

Dental treatment modifications for patients with generalized anxiety disorder should be customized to reflect the degree to which the disorder affects their lives. Whether patients with generalized anxiety disorder have anxiety or phobias about dental treatment or not, dental treatment should progress at a pace and for a duration that does not challenge their emotional endurance. Oral manifestations of long-term anxiety can include destructive parafunctional habits such as bruxism, which can cause excessive wear of the teeth, fractures of existing restorations, temporomandibular joint disorders, and a decrease in the vertical dimension of occlusion. The fabrication of splints or night guards may be required to address these issues.

Anxiety can detract from the patient's desire and ability to maintain optimal oral hygiene. Dental staff should be supportive and use a non-judgmental motivational approach to encourage the patient to maintain an appropriate oral hygiene regimen that may include more frequent recall appointments. Alcohol, prescription drug, and/or illicit drug use may co-occur in patients with generalized anxiety disorder, which can lead to worsening symptoms and a high degree of morbidity and even mortality if left untreated. It is incumbent that dental clinicians discuss their concerns with the patient in an appropriate way and make referrals to mental health care.

PANIC DISORDER

In the United States, 4% to 28% of the population experience panic attacks at some time during their life. The 2.4% annual incidence of panic disorder in the United States is one of the highest prevalence rates worldwide [36; 37].

Panic attacks are most likely to develop in patients who are in their mid-20s and slightly earlier in men than women. Panic disorder age of onset is usually between late adolescence and 35 years of age, while the age of onset for panic disorder with agoraphobia spans the early 20s to early 30s. Panic disorder is more common among women, with a 2:1 ratio and increasing to 3:1 with panic disorder with agoraphobia.

The diagnostic criteria for panic disorder require [5]:

- Recurrent unexpected panic attacks
- One or more of the attacks followed by at least one month of one or both of the following:
  - Persistent concern or worry about additional panic attacks or their consequences
  - Significant maladaptive change in behavior related to the attacks

The symptoms must not be attributable to substance-related effects, other medical conditions, or other psychiatric disorders. Up to 70% of patients report a history of at least one nocturnal panic attack [38]. Patients may present with symptoms suggestive of heightened sympathetic nervous system activity such as palpitations, increased systolic blood pressure, hyperventilation, sweating, or flushing. Other common symptoms include chest pain and discomfort, dizziness, and paraesthesias, while gastrointestinal symptoms such as nausea and vomiting are more common among men [5; 39].

Criteria for panic attacks specify an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes and includes four or more of the following symptoms [5]:

- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath or smothering
- Feelings of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, light-headed, or faint
- Chills or heat sensations
- Paresthesias (numbness or tingling sensations)
- Derealization (feelings of unreality) or depersonalization (being detached from oneself)
- Fear of losing control or going crazy
- Fear of dying

Panic attack is not classified as a mental disorder and does not have a diagnostic code. Instead, an attack can occur with other mental disorders, such as depressive and anxiety disorders, and also be extant with physical disorders.

Medical Treatment

Combined treatment is superior in panic disorder, with effects of combined psycho- and pharmacotherapy treatment versus placebo about twice as large as pharmacotherapy alone versus placebo [40]. The first-line drugs recommended for the treatment of panic disorder are SSRIs or venlafaxine XR [33]. Research suggests that the largest effect size is found with clonazepam, followed by venlafaxine and fluoxetine [41].

The use of medications can only reduce the frequency and intensity of a panic attack but cannot eliminate the situations or places that precipitated the attack. The goal of psychotherapy such as cognitive therapy is to discern the patient's beliefs and perceptions that may serve as the trigger for a panic attack and eliminate them as a source of the heightened anxiety from which a panic attack evolves [42]. The use and duration of medications and psychotherapy will vary according to individual needs.

Oral Health Implications and Dental Treatment Modifications

As discussed, the drugs used to treat panic disorder, specifically antidepressants and benzodiazepines, can interact with other drugs used in dental treatment and result in adverse or unintended effects. These potential interactions should be considered whenever prescribing or administering a medication to these patients.

Dental treatment of patients with panic disorder should begin with a discussion of the patient's medical history that includes the details of the places or situations that have served as triggers for panic attacks. It is also possible that a patient may be unaware that he or she is experiencing what might be a first panic attack. Further complicating the matter, the signs and symptoms can resemble those of serious medical emergencies, including myocardial infarction (heart attack), acute asthmatic attack, or hypoglycemic crisis. In these situations, emergency medical services should be summoned; distinguishing between a panic attack and a medical emergency is beyond the ability of dental professionals.

Conversely, patients with a known history of panic disorder may develop a medical emergency that mimics a panic attack. Patients believed to be experiencing a panic attack should never be left alone, and if there is any doubt as to the origin of the acute symptomatology, emergency medical services should be called.

Patients who experience a panic attack in a dental setting may defer or avoid dental treatment completely and increase their risk of the development of carious lesions and periodontal disease. These patients should be encouraged to continue to seek dental care, with the reassurance that steps can be taken to make the experience less triggering.

SPECIFIC PHOBIA

Specific, simple, or isolated phobia is the excessive or unreasonable fear of (and restricted to) animals, objects, or specific situations (e.g., dentists, spiders, elevators, flying, seeing blood) [31]. Intense anxiety or unexpected panic responses in the presence of specific objects or situations can mark phobia onset but are not the sole causal route. Disgust, either alone or combined with fear, may trigger the onset and maintenance of animal (particularly spiders, snakes, and worms) or blood-injection-injury phobias. This is the most common type of anxiety disorder, with a lifetime prevalence of 15.6% and a past-year prevalence of 12.1% [36].

Women are two to three times more likely to develop phobias than men, with the exception of blood-injection-injury phobia, which is evenly distributed by sex. Roughly 70% of specific phobics report more than one clinically relevant fear. Animals and heights are the most common stimuli, followed by flying, enclosed spaces, and blood-injection-injury. The average age of onset is 7 to 10 years, with declining probabilities of onset into later adulthood. The majority of animal phobias develop before 8 years of age [5; 45; 46]. The average age of treatment engagement is 31 years, although only 8% of persons with specific phobia are reported to seek treatment [46].

Specific, simple, or isolated phobia describes excessive or unreasonable fear in the presence of phobic stimuli, typically involving specific animals, objects, or situations (e.g., dentists, spiders, elevators, flying, seeing blood). Phobic stimuli are either avoided or are endured with significant personal distress [31]. This fear or anxiety must be markedly stronger than the actual threat of the object or situation (e.g., likelihood of being stuck on a well-maintained elevator) [5]. The core features and different types of specific phobia remain unchanged from the DSM-IV, but the requirement was removed that individuals older than 18 years of age must recognize their fear and anxiety as excessive or unreasonable. The duration requirement of longer than six months now applies to all ages [32].

Specific phobias can develop after a traumatic event or from witnessing traumatic events. The fear or anxiety happens every time the person is exposed to the stimulus and may include panic attack symptoms.

The median age of onset with specific phobia is 13 years [5]. According to the DSM-5, specific phobia is diagnosed when the following criteria are met [5]:

- Marked fear or anxiety about a specific object or situation (e.g., flying, seeing blood)

- Phobic object or situation almost always provokes immediate fear or anxiety and is actively avoided or endured with marked fear or anxiety

- Fear or anxiety out of proportion to the actual danger posed by the specific object or situation

- The fear, anxiety, or avoidance is persistent, typically at least six months

- Marked distress or functional impairment

Specific phobia subtypes are organized by phobia categories:

- Animal: Dogs, snakes, insects
- Natural environment: Storms, heights, dark
- Blood-injection-injury: Injections, blood draws, medical/dental procedures
- Situational: Driving, flying, enclosed spaces
- Other: Choking, vomiting, clowns

Medical Treatment

Patients with specific phobias generally do not consult medical professionals when able to avoid the specific feared situations or objects. Exposure therapy is effective in treating specific phobia and is the favored approach. For blood-injection-injury phobias, an effective approach is combining exposure therapy with muscle tension exercises (applied tension) designed to prevent fainting. Using stress-reducing medical devices, such as decorated butterfly needles and syringes, has significantly reduced needle phobia and stress in pediatric and adult patients. With dental phobias, use of cognitive-behavioral therapy can reduce avoidance of oral injections and decrease patient anxiety [47; 48].

Oral Health Implications and Dental Treatment Modifications

It is essential that a discussion that is based on empathy and compassion reveals situations within the dental setting that cause anxiety of such a magnitude that they have precipitated phobia and/or a panic attack in the past for the patient and have the potential to do so in subsequent dental appointments. As noted, modifying treatment and/or devises to reduce stress is recommended to allow dental treatment to proceed.

POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder (PTSD) is a severe, potentially chronic and disabling disorder that develops in some persons following exposure to a traumatic event involving actual or threatened death, serious injury, or sexual assault [49]. Some common symptoms include intrusive thoughts, nightmares and flashbacks of traumatic events, avoidance of trauma reminders, hypervigilance, and sleep disturbance. These symptoms can be highly distressing and substantially impair social, occupational, and interpersonal functioning. The intensely distressing and impairing symptoms of traumatic stress are highly prevalent immediately following traumatic exposure and dissipate over the following days and weeks in most people. Persistence beyond one month post-trauma suggests PTSD [49].

Large community surveys indicate that 50% to 75% of people report experiencing at least one lifetime traumatic event [50]. A U.S. survey from 2001–2003 of 5,692 participants 18 years of age or older found lifetime PTSD prevalence rates of 6.8% overall—3.6% in men and 9.7% in women. Also found were past-year prevalence rates of 3.5% overall, with 1.8% in men and 5.2% in women. These rates were very similar to those of a large survey in the early 1990s that found a lifetime PTSD prevalence rate of 7.8% overall, with 5% in men and 10.4% in women [50].

MEDICAL TREATMENT

The overall objective of PTSD therapy is to treat the four core symptom clusters of intrusive re-experiencing, avoidance, negative alterations in cognitions and mood, and hyperarousal. Psychotherapy is the backbone of PTSD therapy, with pharmacotherapy used as an adjunct if necessary.

Primary care clinicians should be aware of the range of therapeutic options along with their advantages and disadvantages (e.g., time commitment, side effects, risks) and be able to explain these to the patient.

Therapies for PTSD are broadly divided into psychotherapies, pharmacotherapies, and adjunctive or supplemental treatment modalities. Selection of the initial pharmacologic approach is based on clinician and patient choice and guided by the manifesting symptoms of PTSD, other disorders, and patient preference, with polypharmacy choice dictated by clinical presentation and co-occurring psychiatric disorders [51; 52]. SSRIs are widely recommended as first-line agents in the treatment of PTSD [51; 52]. Other possible drug choices include SNRIs, TCAs, monoamine oxidase inhibitors, sympatholytics, benzodiazepines, anticonvulsants, and atypical antipsychotics.

ORAL HEALTH IMPLICATIONS AND DENTAL TREATMENT MODIFICATIONS

Dental clinicians should be aware of these potential adverse drug interactions and side effects of the medications used to treat PTSD when they perform dental procedures and prescribe medications adjunctive to dental treatment. Paroxetine is an SSRI that has been found effective in the short-term treatment of PTSD; however, it has been associated with xerostomia. Normal salivary flow resumes upon discontinuation. The concurrent use of paroxetine and NSAIDs (e.g., ibuprofen, naproxen) can decrease platelet aggregation, and should be avoided if possible. Opioid analgesics may potentiate the effect and toxicity of paroxetine, so their concurrent use should be minimized or avoided [13].

Prior to the initiation of dental treatment for patients with PTSD, it is essential to establish an atmosphere of trust and open communication. In some cases, paranoia or heightened startle reflexes may be present. Patients may associate being placed in a supine position in the dental chair and having their personal space encroached upon by a dental professional with the loss of control experienced during their trauma. An open line of communication will allow for disclosure of these issues and provide a means for resolution.

The efficacy of the patient's oral hygiene should be evaluated at each recall visit, as medication-induced xerostomia can compromise ability to maintain optimal oral hygiene. Hygiene instructions and recall appointments should be tailored to the needs of the patient. Concurrent use and/or misuse of alcohol or recreational/prescribed medications should also be evaluated. A team approach involving the dental and medical team should be used to restore the patient to an ideal level of physical, mental, and emotional health.

SCHIZOPHRENIA

Schizophrenia is a complex psychotic disorder that affects about 1% of the population, with a nearly equal distribution between men and women [53]. Onset occurs later in women compared with men [53]. Symptoms of schizophrenia comprise three broad categories: positive, negative, and cognitive.

Positive symptoms include auditory (most common), olfactory, visual, or tactile hallucinations. Paranoid delusions, delusions of persecution, and grandiose delusions also occur. Thought disorders, characterized by a dysfunctional pattern of thinking, are another type of positive symptom. Finally, movement disorders commonly occur and tend to feature exaggerated and/or agitated body movements.

Negative symptoms are disruptions in normal emotions and behaviors. This may manifest in a variety of emotional issues and behaviors such as flat affect, anhedonia (i.e., a loss of pleasure in the activities of daily life), and difficulty initiating and sustaining activities. Less commonly, patients may display catatonia, with markedly depressed or absent movement and responses.

Cognitive symptoms tend to be more difficult to discern and include poor executive functioning (i.e., ability to understand information and use it to make decisions), difficulty concentrating, and memory issues [54]. A diagnosis of schizophrenia is made when a patient has two or more of the following symptoms for at least one month [5]:

- Hallucinations
- Catatonic movements
- Delusions
- Disorganized speech patterns
- Flattened affect
- Alogia (restricted amount and/or content of speech)
- Disruptions in social or occupational abilities

The exact cause of schizophrenia remains unclear, although a combination of biochemical factors and a genetic influence may contribute. The chance of a child developing schizophrenia is 10% to 13% if one parent has schizophrenia but escalates to 46% if both parents have schizophrenia [55].

MEDICAL TREATMENT

Schizophrenia is a disease with periods of remissions or mild symptoms, but for most patients, it is a long-term, recurring condition. As such, treatment generally continues throughout a patient's life.

Treatment of schizophrenia involves a combination of pharmacotherapy and psychosocial therapy. Most often, medications include typical (first generation) and atypical (second generation) antipsychotics [56]. The most frequently used typical antipsychotics are chlorpromazine, haloperidol, and perphenazine. These medications will address the positive symptoms of schizophrenia, but they do not ameliorate negative symptoms.

ORAL HEALTH IMPLICATIONS AND DENTAL TREATMENT MODIFICATIONS

Xerostomia is a potential adverse effect of antipsychotic medications, with a resumption of normal salivary production upon cessation of use. However, because pharmacotherapy will continue indefinitely, efforts should be made to improve comfort and oral health with saliva substitutes and other palliative interventions.

A more pronounced adverse effect of typical antipsychotic medications is tardive dyskinesia—involuntary movements of the tongue, lips, facial muscles, limbs, and trunk of the body [57]. This adverse effect can take months or years to develop and although it occurs predominantly with the use of the typical antipsychotics, it can also occur with the use of atypical agents.

Tardive dyskinesia is usually mild and reversible; however, it can become severe and irreversible in a small percentage of patients. Benzodiazepines and anticholinergics (e.g., diphenyhydramine) can decrease the intensity of the symptoms, but these agents are also associated with oral and systemic adverse effects. Discontinuing a typical antipsychotic to alleviate the symptoms of tardive dyskinesia can increase the severity of the patient's schizophrenia and should only be done under psychiatric supervision.

In terms of oral health, the involuntary movements of the oral musculature seen with tardive dyskinesia can complicate the patient's ability to eat, speak, swallow, and remain stationary during dental procedures. Spasmodic activity of the intrinsic and extrinsic muscles of the tongue, cheeks, and floor of the mouth can preclude the use of mandibular partial or complete dentures, which rely on a balance of muscular control for their retention. Involuntary movement of the muscles of the soft palate can disrupt the suction seal at the posterior

border of a maxillary denture and compromise the patient's ability to wear this prosthesis. Involuntary muscular activity of the fingers and the hands can present a challenge to maintain optimal levels of oral hygiene, increasing the risk for plaque deposits, dental caries, and periodontal disease. The frequency of recall appointments should reflect the patient's ability to maintain an appropriate level of oral hygiene in the presence of medication-induced xerostomia and/or tardive dyskinesia.

Typical antipsychotics can result in leukopenia, a condition characterized by decreased production of white blood cells (leukocytes) and particularly granulocytic leukocytes (i.e., neutrophils, basophils, and eosinophils) (referred to as agranulocytosis) [13]. Leukocytes are a critical component of an intact immune system and a decrease in production increases the risk for opportunistic oral and systemic infections. For example, impaired immune function can result in the overgrowth of the resident oral fungal organism *Candida albicans*, leading to oral candidiasis. This infection can be refractory to oral antifungal suspensions and systemic antifungal medications. Unchecked, it may extend regionally or systemically, with a high degree of morbidity and even mortality. Similarly, reactivation of herpes simplex virus-1 (HSV) and the development of recurrent herpes labialis is likely with impaired immunity.

Before invasive dental procedures are performed, a complete blood count with differential should be ordered for patients with schizophrenia who are prescribed a typical antipsychotic. The results can help guide decisions to decrease the risk of postsurgical infections and prolong healing.

Chlorpromazine, perphenazine, and haloperidol can potentiate the systemic depressant effects of opioids [14]. If possible, other pain relief methods should be used for patients who use these antipsychotics. Weight gain, dizziness, insomnia, and fatigue are among the more frequently occurring adverse effects of atypical antipsychotics.

Akathisia (a general sense of restlessness) may develop and can interfere with a patient's ability to remain stationary or seated [58]. Even aside from drug side effects, patients with schizophrenia may find it difficult or impossible to remain still in a dental chair for long appointments. As such, shorter appointments may be necessary to complete required dental treatment.

Dysphagia (difficulty swallowing), dysgeusia (distorted perception of taste), and stomatitis (generalized inflammation of the mucosal surfaces of the oral cavity) are also among the potential adverse effects of atypical antipsychotic medications [59]. Patients who wear partial or complete dentures may be unable to use these prostheses in the presence of stomatitis. If eating or swallowing are painful or impossible, liquid nutritional supplements may be necessary. Erosive areas of stomatitis can serve as portals of entry for pathogenic oral microbes, which can lead to local, regional, or systemic infections.

The concurrent use of anxiolytic medications or opioids with risperdone or olanzapine can exacerbate the respiratory depressive effects of the medications, increasing the risk of respiratory arrest [60]. Therefore, these combinations should only be attempted if absolutely necessary and upon approval of the patient's physician.

Dental treatment modifications of schizophrenic patients should be individualized, with consideration of the stability of the patient, current medication(s), and the presence of comorbidities. Consultation with the patient's physician and/or psychiatrist is advisable before beginning dental treatment.

Atypical antipsychotics have been associated with orthostatic hypotension [61]. This can be exacerbated when a patient in a dental chair is raised abruptly from supine to upright position. With this in mind, patients should be raised in a slow, incremental fashion to allow for appropriate regulation of blood pressure.

SOMATIC SYMPTOMS AND RELATED DISORDERS

Somatic symptoms and related disorders are a group of psychiatric conditions in which the patient presents with physical symptoms for which no underlying medical or organic cause can be identified. Previously known as somatoform disorders, the DSM-5 consolidated the number and description of these disorders under the title of Somatic Symptoms and Related Disorders, which will be the term used for this course. The prevalence of somatic symptoms and related disorders is 16.1% to 21.9% in the general population [62]. In order to establish a diagnosis of somatic symptoms and related disorders, the symptoms must [63]:

- Not be explained by a known medical condition, another mental disorder, or by the use of a medication or another substance
- Not be the result of malingering or factitious disorder
- Cause impairment with occupational and social activities or in the activities of daily living

Even with these criteria, establishing a diagnosis of somatic symptoms and related disorders is challenging.

MEDICAL TREATMENT

Treatment for somatic symptoms/disorders involves psychotherapy to identify the ultimate psychogenic etiology. The primary dental treatment concern is the avoidance of unnecessary treatment and referral to the appropriate specialists for patients with these disorders when oral or odontogenic pathology cannot be discerned from a comprehensive clinical and radiographic examination or when these problems are successfully resolved and symptoms persist.

ORAL HEALTH IMPLICATIONS AND DENTAL TREATMENT MODIFICATIONS

Pain Disorder

Pain disorder is considered a somatic disorder characterized by pain for which no organic or physical etiology can be identified. In patients with this disorder, psychologic factors such as stress, anxiety, and depression usually precede the onset of pain and can influence its severity and duration. The perception of pain can occur anywhere, including the oral and maxillofacial complex. Patients may complain of odontogenic pain even after a complete radiographic survey and clinical examination rules out dental caries, endodontic pathology, and defective restorations.

Atypical facial pain can be of varying durations and can occur in varying locations. Common oral manifestations of pain disorder include atypical facial pain and oral dysesthesia [64]. The pain may be described as burning or tingling, sharp, dull, or as a sensation of pressure or crushing [65]. Other conditions that can cause an oral burning sensation (e.g., vitamin B12 deficiency, erythematous candidiasis) should be ruled out before a somatic disorder is considered.

It is important not to equate the absence of obvious oral or odontogenic pathology with a somatic disorder. Likewise, providing dental treatment and/or analgesic prescriptions is not recommended without knowledge of the underlying cause of pain. When there is no apparent etiology for expressed pain, referral to another healthcare professional (e.g., an oral surgeon, primary care physician, neurologist) should be given to determine if the pain has an etiology beyond the oral and maxillofacial complex.

Hypochondriasis

Hypochondriasis is a somatic disorder in which the patient is convinced that his/her physical symptoms are indicative of a life-threatening medical condition. Hypochondriasis affects 2% to 7% of the population, and its diagnosis is made if the patient maintains a nondelusional preoccupation with the symptoms for at least six months [63]. In the dental setting, a patient who has pain in the oral-pharyngeal area may be convinced the pain originates from malignancy.

If a thorough clinical and radiographic exam detects pathology (e.g., caries, periodontal disease, oral lesions, endodontic pathology), these issues should be treated first. If a patient's symptoms persist upon the successful resolution of these problems and in the absence of any other evident pathology, the patient should be referred to a specialist. Patients with hypochondriasis may not be reassured even if clinical examinations and tests do not reveal any further pathology.

SUBSTANCE USE DISORDERS

Substance use disorder (SUD) is considered a mental illness and can undermine individuals' physical, psychologic, social, and emotional health and safety. The DSM-5 identifies 10 classes of drugs that may be linked to an SUD: alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics or anxiolytics, stimulants, and nicotine (tobacco) [5]. Although they are outlined individually, individuals may have more than one SUD concurrently.

Diagnosis of SUD is made when at least two of the following symptoms within a 12-month period [5]:

- Use or consumption of more of a substance than planned
- Inability to control or stop use
- Spending an extensive amount of time using the substance(s) and using any means to obtain it/them

- Continued substance use results in failure to fulfill personal and professional obligations
- Cravings for the substances(s)
- Continued use of the substance(s) despite emerging or worsening health problems
- Continued use of the substance(s) despite a negative impact on personal or professional relationships
- Use of the substance(s) in dangerous situations such as driving or using heavy machinery
- Withdrawing from activities because of substance use
- Developing a tolerance to the substance(s) used, defined by:
  - A need for markedly increased amounts to achieve intoxication or desired effect
  - A markedly diminished effect with continued use of the same amount
- Experiencing withdrawal symptoms when the use of the substance(s) stops

SUDs transcend geographic boundaries, sex/gender, race, ethnicity, and socioeconomic status. It is important to remember that SUD is a mental illness and not a character flaw or the result of a lack of willpower. Patients with a SUD should be treated with the same empathy and concern conveyed to any patient with a mental illness.

It is important to understand some of the most common terms used when discussing SUDs. Addiction is defined by the American Society of Addiction Medicine (ASAM) as "a primary chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing the development and manifestations" [66]. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Addiction is also referred to as psychologic dependence.

Tolerance refers to the diminishing effect of a substance over time. A patient has developed tolerance if it takes an increased dose of the drug to illicit the same effects. The term dependence has replaced the term "addiction" in some contexts. Substance dependence refers to both psychologic dependence (or addiction) and physical dependence. Physical dependence consists of neurobiologic adaptation (development of tolerance) from chronic exposure.

Most dental clinicians will treat a patient with a SUD during their careers. If a patient is suspected of having an SUD, it is imperative to be nonjudgmental and empathetic in discussions with the patient and to provide a pathway for the patient to receive appropriate treatment.

Specific drugs of abuse will have different effects on users. All dental professionals should have knowledge of the most commonly abused drugs, their systemic and oral effects, and best practices when providing care to these patients. The following sections introduce the most common SUDs encountered in dental practice.

OPIOID USE DISORDER

Few medications have been highlighted as much in recent years as opioid analgesics. This is largely due to the high risk of misuse and diversion associated with these medications. However, the first reference to opium is found in the 3rd century B.C.E. The use of opium was well-understood by Arab physicians, and Arab traders introduced the drug to Asia, where it was utilized primarily for the control of dysentery [67].

The isolation of morphine from opium was achieved in 1806 and was named for Morpheus, the Greek god of dreams [67]. The discovery of other alkaloids in opium followed: codeine in 1832 and papaverine in 1848. By the mid-nineteenth century, pure alkaloids were used in medical practice in place of crude opium preparations [67].

In addition to the highly beneficial therapeutic effects, the toxic side effects and addictive potential of opioids have been known for centuries. These undesired effects have prompted a search for a potent synthetic opioid analgesic free of addictive potential and other complications. However, all synthetic opioids introduced into medical use share the same liabilities of the classical opioids. The search for new opioid therapeutics has resulted in the synthesis of opioid antagonists and compounds with mixed agonist-antagonist properties, such as buprenorphine, which has expanded therapeutic options and provided the basis of expanded knowledge of opioid mechanisms [67].

Nonmedical use of prescription opioids was reported in literature as early as 1880. A report in 1928 documented that injection of opioids contributed to the development of nonmedical use and misuses of prescription opioids. Before 1930, the prevalence of nonmedical opioid injecting in the United States was low. But by the mid-1940s, more than one-half the admissions to the National Institute of Mental Health's Lexington Hospital were for the misuse of prescription opioids [68].

Opioid broadly refers to all compounds related to opium. The term opium is derived from *opos*, the Greek word for "juice," as the drug is derived from the latex sap of the opium poppy *Papaver somniferum*. Drugs derived from opium, including the natural products morphine, codeine, and thebaine, may be referred to as opiates [67]. However, for the purposes of simplification, all compounds will be referred to as opioids in this course.

OPIOID ANALGESIC APPROXIMATE DOSE EQUIVALENTS			
Opioid Analgesic	Oral Dose	Parenteral Dose	Morphine Equipotency Ratio, Oral
Morphine	30 mg	10 mg	Reference opioid
Codeine	200 mg	100 mg	Not established
Fentanyl (transdermal)	Not applicable	100 mcg	Not applicable
Hydrocodone (Zohydro ER)	30–45 mg	Not applicable	1.5:1
Hydromorphone (Exalgo ER)	8 mg	2 mg	5:1
Levorphanol	4 mg	2 mg	Not established
Oxycodone (OxyContin ER)	20–30 mg	10–15 mg	2:1
Source: [69; 70]			*Table 1*

Morphine is the reference against which other opioids are compared, and analgesic potency is calculated as dose equivalence to morphine (i.e., morphine milligram equivalent or MME). *Table 1* shows a typical equianalgesic-dose table with figures validated for acute pain in opioid-naïve patients and conversions for opioid-tolerant patients [70].

Morphine and most other opioid agonists share in common the following physiologic effects [67]:

- Analgesia
- Changes in mood and reward behavior
- Disruption of neuroendocrine function
- Alteration of respiration
- Changes in gastrointestinal and cardiovascular function

Pharmacology

Opioids have been the mainstay of pain treatment for thousands of years, exerting their effects by mimicking naturally occurring endogenous opioid peptides or endorphins [67]. Although many new opioids have been developed with pharmacologic properties similar to morphine, morphine remains the standard against which new analgesics are measured [67].

Endogenous Opioid Peptides

The endogenous opioid system is complex and subtle, with diverse functions. The system plays a sensory role, which is prominent in inhibiting response to painful stimuli; a modulatory role in gastrointestinal, endocrine, and autonomic functions; an emotional role evidenced by the powerful rewarding and addicting properties of opioids; and a cognitive role involving modulation of learning and memory [67].

There are three distinct families of classical opioid peptides: enkephalins, endorphins, and dynorphins. Each of these families is derived from a distinct precursor protein and has a characteristic anatomical distribution. The precursor proteins, preproenkephalin, pro-opiomelanocortin (POMC), and preprodynorphin are encoded by three corresponding genes. The primary opioid peptide derived from POMC is beta-endorphin. The POMC precursor is also processed into the non-opioid peptides adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (alpha-MSH), and beta-lipotropin (beta-LPH), suggesting a common precursor for the stress hormone ACTH and the opioid peptide beta-endorphin. This association indicates a shared physiologic linkage between the stress axis and opioid systems, which has been validated by the observation of stress-induced analgesia [67].

Opioid Receptors

Opioids produce their effects through activity at three major receptor subtypes: mu, kappa, and delta. These G-protein-coupled receptors are linked to adenylate cyclase. The endogenous ligands for these receptors, beta-endorphin, enkephalin, and dynorphin, are expressed heterogeneously throughout the central and peripheral nervous systems, with a distribution pattern parallel with that of opioid receptors. Opioid receptors are also found in the central respiratory centers. Functional studies have revealed substantial parallels between mu and delta receptors and dramatic contrasts between mu/delta and kappa receptors [71].

Most opioid therapeutics, and all opioids with abuse potential, are selective for mu receptors, reflecting their similarity to morphine. However, drugs that are relatively selective at standard doses can interact with additional receptor subtypes at higher doses, resulting in divergent pharmacologic profiles [67]. A large number of endogenous ligands activate a small number of opioid receptors, a pattern strikingly different from most other neurotransmitter systems, in which a single ligand interacts with a large number of receptors that have different structures and second messengers [67].

Absorption, Distribution, Metabolism, and Elimination

Typically, opioids are readily absorbed from the gastrointestinal tract. The more lipophilic opioids are easily absorbed through the nasal or buccal mucosa. The most lipophilic opioids can be absorbed transdermally [67]. Most opioids, including morphine, undergo variable but significant hepatic first-pass metabolism, limiting oral bioavailability relative to parenteral administration. Most opioids act quickly when given intravenously. Compared with more lipid-soluble opioids, such as codeine, heroin, and methadone, morphine crosses the blood-brain barrier at a considerably lower rate [67].

Risk Factors for Opioid Use Disorder

Persons at heightened risk for heroin experimentation include those who abuse alcohol or marijuana, those with first-degree relatives addicted to alcohol or other drugs, and those with friends and associates addicted to heroin or at high risk of heroin experimentation [72]. Of course, not all persons who use drugs regarded as having a high liability of abuse and dependence end up becoming addicted to the drug. Among persons who try heroin, an estimated 23% develop heroin dependence, a rate comparable to cocaine but greater than cannabis [73].

The expected drug effect and the setting of use (context of administration) play important roles in the social learning of drug use. Because opioids, like other drugs that increase dopamine turnover, lead to conditional responses, the use of opioids may become conditioned to the activities of daily living. As a result, environmental stimuli become powerfully associated with opioid use, which can trigger cravings for the drug [74]. The visibility of pharmaceutical marketing and advertising of medications may also play a role by changing the attitudes towards ingestion of these agents [74]. For youth, a social learning aspect to drug use is likely, based on the modeling of drug use by adults in their families and social networks [74].

Individuals who use nonmedical prescription opioids before 13 years of age are more likely to become addicts than those who initiated use at 21 years of age or older. The odds of becoming an addict are reduced 5% each year after 13 years of age [75]. Additionally, it is a commonly held view among adolescents (27%) that prescription drugs are "much safer" than street drugs [76]. This belief is undoubtedly shared with much of the adult population and has led to the extraordinary rise in recreational prescription drug users.

Dental Treatment Considerations

Responsible prescribing of opioids is an essential measure to avoid contributing to and escalating the opioid crisis in the United States. Opioid analgesics are generally not used as first-line analgesic therapy; non-drug and non-opioid drug alternatives should be considered first. Opioids may be initiated when benefits are likely to outweigh risks, when other approaches to analgesia are ineffective or unlikely to be effective, and with a treatment plan reasonably designed to mitigate the risks of addiction, toxicity, and other adverse effects.

Dental pain after oral or periodontal surgery is caused by the release of prostaglandins from injured tissues. This type of pain in generally best managed by nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin formation. NSAIDs act locally while opioids act centrally, which results in greater and more dangerous side effects. Several controlled studies have concluded that NSAIDs with or without adjunctive acetaminophen provide equivalent or superior dental pain relief than opioids [77]. The recommended dose of ibuprofen for mild post-procedural dental pain is 200–400 mg every four to six hours; alternatively, 400–600 mg ibuprofen combined with 500 mg acetaminophen every six hours may be used. If severe pain develops and an opioid analgesic is indicated, it is vital to start with the lowest possible dose for three days, after which the patient can be switched to ibuprofen with or without acetaminophen [78]. The American Dental Association supports statutory limits on the dosage and duration of opioid analgesics of no more than seven days for the treatment of acute dental pain [79]. Dental clinicians can also use techniques, including atraumatic surgical technique and long-lasting local anesthetics (e.g. bupivacaine), to minimize postprocedural pain and the need for analgesia.

If an opioid use disorder is disclosed or suspected, steps should be taken to increase patient safety and minimize the risk of misuse and dependence. In patients with opioid use disorder, nitrous oxide inhalation analgesia should be avoided, as it creates a similar pleasurable effect to opioids and can increase cravings. Benzodiazepines have become a popular adjunct medication to reduce dental-related anxiety ("sleep dentistry"), but coingestion of opioids and this class of medications elevates the risk of pronounced respiratory depression and fatality [80].

Patients with opioid use disorder are more prone to the development of xerostomia, caries, periodontal disease, and oral infections [61]. As discussed, the decreased flow and volume of saliva associated with xerostomia reduces the self-cleaning action of the teeth, increasing the risk of dental caries and periodontal disease.

Although the patient's medical history is reviewed prior to any dental treatment, he or she may not disclose current or historical opioid misuse or addiction. If a patient has a suspected opioid use disorder, the clinician should initiate an open, judgement-free discussion that focuses on the long-term well-being of the patient. Through responsible prescribing practices and patient referral, if appropriate, dental clinicians can help address the opioid crisis and provide the best level of patient care.

BENZODIAZEPINE USE DISORDER

For years, anxiolytic medications have been used in dental practice to decrease anxiety and allow treatment to be provided comfortably. Benzodiazepines provide a level of sedation that allows for significant relaxation but continued response to verbal commands and questions. Outside of dental practice, these agents may be used in the treatment of insomnia, generalized anxiety disorders, convulsive disorders, and seizure disorders. However, benzodiazepines are associated with potential problems with abuse and addiction.

Benzodiazepines are CNS depressants that enhance the major inhibitory neurotransmitter gammaaminobutyric acid (GABA) and decrease brain activity [82]. Benzodiazepines are distinct in their potentially lengthy duration of action; some agents produce active metabolites that extend their pharmacologic effect.

When used in dental practice, benzodiazepines are prescribed for a short period, usually just the night before and/or immediately preceding the appointment. Often, diazepam 5–10 mg is used for this purpose. The primary concern with diazepam is its extended duration of action, especially if opioids are also prescribed for postprocedural pain. Diazepam is metabolized as the active metabolite desmethyldiazepam, the half-life of which is 100 hours [13]. This prolonged duration of action far exceeds the duration of a dental appointment and can leave the patient in a sedated state with decreased mental acuity. It can also interact with opioid analgesics to potentiate the sedating and respiratory depression effects.

The ideal anxiolytic medication for dental appointments would provide adequate sedation with a short half-life. As such, triazolam is a better option, with a plasma half-life of two to three hours and rapid clearance that allows the patient to resume regular activities quickly [83]. Patients should be advised to refrain from alcohol while taking benzodiazepines because of the risk for CNS depression.

At the dose and duration benzodiazepines are used in dental practice, addiction and withdrawal symptoms are unlikely. However, some dental patients are on long-term benzodiazepine therapy for a mental health disorder (e.g., generalized anxiety disorder). The long-term use of these medications is associated with the potential for tolerance, physical dependence, addiction, and withdrawal symptoms.

Among patients who have used benzodiazepines for longer than six months, approximately 40% will experience moderate-to-severe withdrawal symptoms; the remaining 60% will experience mild symptoms upon abrupt cessation [84]. The most common benzodiazepine withdrawal symptoms include anxiety, panic attacks, insomnia, nightmares, depression, night sweats, heart palpitations, muscle pain, and problems with memory and concentration [85].

Dental Treatment Considerations

If a dental patient is known to be on long-term benzodiazepine therapy, consultation with the his or her physician or psychiatrist may be required to ensure that the medication can be safely continued or halted. As discussed, opioid analgesics should be avoided if possible in these patients. Similarly, nitrous oxide inhalation sedation can enhance the CNS depressant effects of benzodiazepines and should be avoided.

Withdrawal from benzodiazepines must be done under medical supervision and usually features a gradually decreasing dose. The expected severity of withdrawal from benzodiazepines can be assessed using the Clinical Institute Withdrawal Assessment—Benzodiazepines (CIWA-B) tool, which consists of 22 items. Higher scores indicate increasing difficulty and morbidity with the withdrawal symptoms [85].

Although there are no oral lesions specific to benzodiazepine use, xerostomia is a potential adverse oral effect. Personalized oral hygiene instructions and a more frequent recall schedule can promote optimal oral health for patients who experience this adverse effect. Consultation with the patient's physician should be sought if there is any concern about the patient's ability to withstand dental treatment.

ALCOHOL USE DISORDER

No substance, legal or illegal, has a more paradoxical mythology than alcohol. It is undeniably one of the most widely and safely used intoxicants in the world; however, it is also potent and dangerous, both from a psychologic and a physiologic viewpoint. Alcohol is currently responsible for more deaths and personal destruction than any other known substance of abuse, with the exception of tobacco. Substances of abuse are often put into categories based on their effects. Alcohol has effects similar to other depressants. Characteristics include:

- Decreased cognitive function while intoxicated
- Decreased inhibition and increased impulsivity
- Risk of overdose
- Development of depressive symptoms in heavy users
- Withdrawal symptoms similar to other depressants
- Symptoms of anxiety during withdrawal
- Substance-induced psychoses in some heavy users

There are several known risk factors for alcohol use disorders, including [86; 87]:

- Temperament: Moodiness, negativity, and provocative behavior may lead to a child being criticized by teachers and parents. These strained adult-child interactions may increase the chances that a child will drink.
- Hyperactivity: Hyperactivity in childhood is a risk factor for the development of adult alcohol use disorders. Children with attention deficit hyperactivity disorder (ADHD) and conduct disorders have increased risk of developing an alcohol use disorder. Childhood aggression also may predict adult alcohol abuse.

- Parents: The most compelling and largest body of research shows parents' use and attitudes toward use to be the most important factor in an adolescent's decision to drink.
- Gender: Among adults, heavy alcohol use is almost three times more common among men than women and also more common among boys in middle or high school than among girls. Men with ADHD and/or conduct disorders are more likely to use alcohol than men without these disorders, while women who experience more depression, anxiety, and social avoidance as children are more likely to begin using alcohol as teens than women who do not experience these negative states.
- Psychology: Bipolar disorder, schizophrenia, antisocial personality disorder, and panic disorder all also increase the risk of a future alcohol use disorder.

Alcohol use disorder is a primary and chronic disease that is progressive and often fatal; it is not a symptom of another physical or mental condition. It is a disease in itself, like cancer or heart disease, with a very recognizable set of symptoms that are shared by others with the same disorder. About 15.1 million people in the United States met DSM-5 criteria for alcohol use disorder in 2015, with an additional 2.6 million abusing or dependent on both alcohol and illicit drugs [88].

Dental professionals should understand the criteria and warning signs of alcohol use disorder. This enables safe patient care and earlier confrontation and intervention. Verifying the facts that show a person is at risk for alcohol use disorder and confronting the impaired individual with those facts is the definition of an office or brief intervention. Brief intervention is most effective before dependence is reached. Once diagnosable, the patient needs more comprehensive intervention.

Dental Treatment Considerations

Alcohol consumption can affect a variety of physiologic and psychologic processes, and persons who are currently inebriated should have dental treatment deferred. Although alcohol use disorder is not associated with any specific oral lesions, there are several areas of oral involvement that may be associated with excessive and/or long-term alcohol consumption. Excessive drinking may interfere with the absorption, digestion, metabolism, and utilization of nutrients, particularly vitamins. Individuals with alcohol use disorder often use alcohol as a source of calories to the exclusion of other food sources, which may also lead to a nutrient deficiency and malnutrition. In the late stage of the disease, patients may develop anorexia or severe loss of appetite, and refuse to eat. Persons with alcohol use disorder account for a significant proportion of patients hospitalized for malnutrition [89].

Direct toxic effects of alcohol on the small bowel causes a decrease in the absorption of water-soluble vitamins (e.g., thiamine, folate, B6). Studies have suggested that alcoholism is the most common cause of vitamin and trace-element deficiency in adults in the United States. Alcohol's effects are dose dependent and the result of malnutrition, malabsorption, and ethanol toxicity [90]. Vitamins A, C, D, E, K, and the B vitamins are deficient in some individuals with alcohol use disorder. All of these vitamins are involved in wound healing and cell maintenance. Because vitamin K is necessary for blood clotting, deficiencies can cause delayed clotting and result in excess bleeding. Vitamin A deficiency can be associated with night blindness, and vitamin D deficiency is associated with softening of the bones. Deficiencies of other vitamins involved in brain function can cause severe neurologic damage (e.g., deficiencies of folic acid, pyridoxine, thiamine, iron, zinc). Thiamine deficiency from chronic heavy alcohol consumption can lead to devastating neurologic complications, including Wernicke-Korsakoff syndrome, cerebellar degeneration, dementia, and peripheral neuropathy [91].

Alcohol abuse is a major risk factor for many infectious diseases [92]. While respiratory infections are the most common, opportunistic oral infections may also occur, including candidiasis, angular cheilitis, necrotizing ulcerative gingivitis, and recurrent herpes labialis. Odontogenic infections of pulpal and/or periodontal origin are more virulent in persons with compromised immune systems and can have an aggressive extension into deeper fascial and muscle layers, with the potential for serious morbidity. Infections of rapid onset and regional dissemination require intravenous antibiotics and may require hospital admission. Dental clinicians who observe these opportunistic oral infections should discuss the finding with the patient.

Chronic alcohol abuse can also have an adverse effect on the salivary glands. In some cases, this manifests as bilateral enlargement of the parotid glands, known as sialosis. Sialosis is the result of peripheral neuropathy induced by chronic exposure to ethanol and reduced salivary flow [61].

A decrease in the buffering ability of the saliva results in a more acidic environment and proliferation of caries and *Candida albicans*. Prescription-strength fluoride toothpaste or gels can help reduce this risk.

The teeth of an individual with alcohol use disorder may be eroded due to the repetitive chemical (acidic) exposure to alcoholic drinks or vomit, resulting in perimolysis. The process of dental erosion can affect any tooth but the palatal surfaces of the maxillary teeth are most frequently affected.

The classic presentation of an eroded tooth surface is smooth and shiny surface dentin. This exposed dentin can be sensitive to thermal changes and sweets. Erosive wear can undermine dental restorations and lead to a progressive loss of the vertical dimension of occlusion. Teeth with extensive loss of enamel can be difficult to restore.

The long-term abuse of alcohol can cause bone marrow suppression [93]. This can lead to a diminished number of neutrophils, which have a critical role in phagocytize bacteria associated with periodontal disease. This deficiency can predispose individuals with alcohol use disorder to opportunistic infections and more severe periodontal disease.

A deficiency in the quantity or the quality of platelets can impair the ability to obtain hemostasis after oral surgery, periodontal surgery, or root planing and curettage. Conducting a complete blood count (CBC) with differential can determine if platelet levels are sufficient to obtain hemostasis. However, these tests are not easily accessible for many dental practices. Patients can be asked if they bruise easily, if they experience problems with postprocedural bleeding after other invasive procedures, if they have a history of spontaneous nose bleeds, or if a small cut requires an extended time to coagulate. A positive response to any of these questions could indicate a problem with coagulation/healing and should prompt referral to a physician for further testing. Any invasive dental procedures should be deferred.

The liver is a particularly vulnerable organ to alcohol consumption, in large part because it is where alcohol is metabolized prior to elimination from the body. The most common manifestation among persons with alcohol use disorder is called "fatty liver." Among heavy drinkers, the incidence of fatty liver is almost universal. For some, a fatty liver may precede the onset of alcoholic cirrhosis.

The liver is the most critical organ for the metabolism of medications most commonly used in dental treatment, including analgesics, antibiotics, and local anesthetics. Amide-type local anesthetics (e.g., lidocaine, mepivacaine, prilocaine bupivacaine) are metabolized in the liver, and compromised hepatic function can cause plasma levels of local anesthetic to increase to toxic levels. As such, the lowest dose of local anesthetics should be used for these patients. Articaine is technically classified as an amide, but approximately 90% to 95% is metabolized by plasma esterases [94]. So, articaine is preferred for patients with compromised hepatic function, if appropriate.

Chronic heavy drinking appears to activate the enzyme CYP2E1, which may be responsible for transforming the over-the-counter pain reliever acetaminophen into toxic metabolites that can cause liver damage [95]. Even when acetaminophen is taken in standard therapeutic doses, liver damage has been reported in this population [96; 97]. A review of studies of liver damage resulting from acetaminophen-alcohol interaction reported that, in individuals with alcohol use disorder, these effects may occur with as little as 2.6 grams of acetaminophen (four to five "extra-strength" pills) taken over the course of the day by persons consuming varying amounts of alcohol [98]. The damage caused by alcohol-acetaminophen interaction is more likely to occur when acetaminophen is taken after, rather than before, the alcohol has been metabolized [99]. Moderate drinkers should also be made aware of this potential for interaction. There is now a warning label on the bottle that states, "If you consume three or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers." Further, in 2014, the FDA issued a statement that combination prescription pain relievers containing more than 325 mg acetaminophen per dosage unit should no longer be prescribed due to reported severe liver injury with acetaminophen in patients who took more

than the prescribed dose in a 24-hour period; took more than one acetaminophen-containing product at the same time; or drank alcohol while taking acetaminophen products [100].

NICOTINE (TOBACCO) USE DISORDER

Nicotine dependence is considered a SUD and is the component of all tobacco products. Most commonly, nicotine is self-administered via cigarette smoking. Cigarette smoking is on the decline in the United States, but use of other tobacco products is not [101]. In addition to a rise in use of smokeless tobacco, people across the United States (especially youth) are using e-cigarettes, cigars, cigarillos (small cigars), hookahs, kreteks, pipes, and bidis (or beedis) [102; 103]. Unfortunately, each of these products is just as dangerous (if not more so) as use of cigarettes.

The rise of e-cigarettes in the past decade has introduced new variables in the prevention and treatment of nicotine addiction. Originally marketed as a smoking cessation tool, e-cigarettes are electronic products that typically deliver nicotine in the form of an aerosol [104].

Cigarette smoke is a complex mixture of more than 7,000 components, including nicotine, aromatic hydrocarbons, sterols and oxygenated isoprenoid compounds, aldehydes, nitriles, cyclic ethers, and sulfur compounds [105; 106; 107]. At least 70 of these components are known to cause cancer [107].

Because nicotine can be absorbed through the oral mucosa, it does not have to be inhaled to enter the bloodstream [61]. In fact, smokeless tobacco users absorb two to three times the amount of nicotine absorbed from smoking. Smokeless tobacco is defined as tobacco products that are sucked or chewed (not burned) and includes chewing tobacco, snuff, and dissolvables. An esti-mated 8.6% of rural adults use smokeless tobacco, compared with 6% of urban adults [108]. Rates of smokeless tobacco use are greatest in states with large rural areas: Wyoming, West Virginia, Arkansas, and Montana [109]. Results of studies suggest that factors other than age, gender, poverty level, and region are driving urban-rural differences in tobacco use. In one study, the most likely reasons given for smokeless tobacco use were affordability, choice of flavors, ability to use in public places (as opposed to smoking), and safety to persons around the user (i.e., no secondhand smoke) [110]. As noted, while there may be a perception that these products are safer than smoked tobacco, they contain nicotine, are highly addictive, and have been linked to oral, esophageal, and pancreatic cancers [111].

Cigarettes deliver nicotine in a pulsatile manner, with plasma concentrations reaching their peak within 1.5 to 3 minutes of the commencement of smoking and gradually returning toward baseline within two to three hours [112]. Thus, nicotine levels rise and fall throughout the day with each cigarette smoked, declining to minimum amounts found in nonsmokers in the morning after the extended abstinence period of sleep. Such continuous flux in blood nicotine levels locks the user into an endless cycle of ups and downs and is thought to lead to the commonly held notion that smoking has a positive effect on mood. Considering smokers begin to experience withdrawal symptoms within hours of their last cigarette, and because these unpleasant effects are almost completely alleviated by smoking, this perception is hardly surprising. Daily repetition of this process links these perceived positive health benefits to the act of smoking in the smoker's mind and often results in the false identification of cigarettes as an effective form of self-medication [113].

Smoking and tobacco use is associated with a variety of chronic and potentially fatal illnesses. In particular, smoking has been implicated in the development of malignant and nonmalignant lung disease, including chronic obstructive pulmonary disease, bronchitis, influenza, emphysema, pneumonia, and lung cancer. Cardiovascular disease, defined as acute myocardial infarction (MI) and stroke, is strongly related to smoking and comprises 34% of smoking-related mortality; conversely, smoking yields 16% of cardiovascular-related mortality [105].

Oral Implications

In addition to the many deleterious systemic effects of nicotine and smoking, tobacco can have serious adverse effects on oral health as well. Some are reversible and relatively mild, such as teeth staining, while others can result in serious morbidity and mortality, including oral and oropharyngeal squamous cell carcinoma.

Tobacco residue leaves a sticky film on the teeth, which causes staining but also can retain bacterial plaque and increase the risk of caries and periodontal disease. Composite restorations can also be stained by tobacco, especially if there are surface porosities and/or irregularities. Depending on the depth and extent of staining, it may be necessary to replace restorations. Smokers should be advised to adhere to strict oral hygiene practices and recall schedule.

The soft tissues of the oral cavity and throat are also affected by prolonged exposure to tobacco via smoking or chewing. Some of the most common adverse effects associated with tobacco use are gingival recession, mucosal lesions (e.g., leukoplakia), delayed healing of surgical sites, and discoloration of the dorsum of the tongue [114]. Nicotine stomatitis (a widespread palatal keratosis) is most common among heavy pipe and cigar smokers and is a chronic inflammatory response of the palatal minor salivary glands.

Of course, the most dire oral consequence of tobacco use is oral cavity squamous cell carcinoma (OCSCC). Each year, there are more than 54,000 new cases and 10,000 deaths from OCSCC or related complications [115]. Many cases of OCSCC are diagnosed at advanced stages with significant local and regional metastases, and the related surgical resection and radiation therapy necessary for advanced-stage OCSCC are associated with a high degree of morbidity and mortality. Tobacco use is the most commonly identified risk factor for the development of OCSCC, and tobacco users have a 5- to 25-fold higher risk of the development of these malignancies compared with nonusers [116]. While both smoking and chewing tobacco increase the risk for oral malignancy, the sustained direct exposure seen with smokeless tobacco use is a greater risk. This risk is increased with concurrent alcohol consumption, as alcohol desiccates the mucosal surface and allows the carcinogens in tobacco to have an extended contact time with the tissues.

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EVIDENCE-BASED
PRACTICE
RECOMMENDATION

The American Dental Association asserts potentially malignant disorders can be diagnosed clinically as leukoplakia, erythroplakia, erythroleukoplakia, or submucous fibrosis, and these lesions may occur among heavy tobacco and alcohol users.

(https://jada.ada.org/article/S0002-8177(17)30701-8/fulltext?dgcid=PromoSpots_EBDsite_Oralcancer. Last accessed February 15, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

Early identification of the lesions of OCSCC is essential. Dental clinicians should provide thorough oral cancer screenings on all of their patients, and lesions that have not healed within two weeks after discovery or those that are highly suspicious should be biopsied. Unfortunately, the lesions of OCSCC can present in a variety of ways—there is no characteristic or diagnostic lesion. Leukoplakic (white) lesions are more common than the erythroplakic (red) lesions, but the latter has a much higher potential for malignant transformation.

Other possible adverse oral effects of smokeless tobacco use include gingival recession, halitosis, enamel erosion, damage to the alveolar bone, and periodontal disease. There is also an increased risk for coronal and root surface dental caries, because sugar is added to smokeless tobacco products [117].

Given the extensive potentially detrimental effects of tobacco use, all healthcare professionals including dental professionals, should counsel their patients to stop tobacco use. U.S. Public Health Service guidelines recommend that all patients be asked [118]:

- Do you smoke or chew tobacco?
- Would you like to quit?

If a patient wants to quit, draw upon the same armament of strategies used to help motivate other health behavior change, such as brushing, flossing, and attending recall appointments. In addition, tobacco cessation programs and pharmacologic agents are often effective. For patients who are not ready to quit, employ the strategies for people in the precontemplative stage of change—remain nonjudgmental and find neutral ways to raise awareness of the problem.

Nicotine replacement therapy is effective in helping people stop tobacco use. This includes patches, gum, lozenges, inhalers, and nasal spray. Bupropion was the first non-nicotine pharmacotherapy for the treatment of tobacco dependence with proven efficacy [119]. Cessation rates have been reported to improve when drug therapy combines nicotine replacement with the antidepressant bupropion [120; 121]. However, in its 2020 guideline for initiating pharmacologic treatment of tobacco-dependent adults, the American Thoracic Society (ATS) recommends varenicline over both bupropion and a nicotine patch for tobacco-dependent adults. In adults who are not ready to discontinue tobacco use, the ATS recommends beginning treatment with varenicline rather than waiting until patients are ready to stop tobacco use [119]. It is important to note that these medications have been associated with adverse effects, including an increased risk for depression and suicide [13].

Not surprisingly, tobacco cessation has high rates of relapse, and most people require multiple quit attempts to remain permanently tobacco-free. After 12 weeks of abstinence, about 43% of people return to regular use. However, longer periods of abstinence increase long-term success rates. After five years of abstinence, relapse rates drop to about 7% [122]. This presents an opportunity to help patients understand that tobacco cessation is a long-term process and previous attempts provide learning opportunities for the next attempt.

CANNABIS USE DISORDER

Cannabis products such as marijuana and hashish comprise the most widely used recreational drugs both in the United States and worldwide [123]. Although, with a few exceptions, these drugs lack the liability of abuse and dependence seen with other illicit drugs, such as cocaine, methamphetamine, and heroin, physical and psychologic withdrawal symptoms can occur with cannabis products, posing an additional consideration in the management of these patients.

There are several species of cannabis, including *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. *Cannabis sativa* is the most widely used variety and can be cultivated in a variety of climates [124; 125]. The two main derivatives of cannabis are marijuana and hashish. The term marijuana originated in Mexico to describe cheap tobacco; today, it refers to the dried leaves and flowers of the *Cannabis* plant. Hashish, an Arabic term, is the viscous resin of the plant [124; 125].

Cannabis contains more than 480 known chemicals, more than 100 of which are grouped under the category of cannabinoids [124; 126]. The primary psychoactive ingredient is delta-9-tetrahydrocannabinol (delta-9-THC), which accounts for up to 25% of the total dry weight of high-potency strains [127]. Other cannabinoids, including delta-8-THC, cannabinol, cannabicyclol, cannabichromene, and cannabigerol, are present in small quantities (typically less than 5% dry weight) and have no significant psychotropic effects compared to THC. It is unknown whether these compounds may have an impact on the overall effect of cannabis [124]. One notable exception is cannabidiol (CBD), which in some cannabis strains can account for up to 5% dry weight and has demonstrated therapeutic efficacy for psychosis, anxiety, and other disorders [127; 128; 129].

Cannabis use disorder is best described as a chronic relapsing disease characterized by compulsive seeking and use of cannabis, accompanied by functional and molecular changes to the brain [5]. The single most defining aspect of cannabis use disorder is the salience of the relationship with the drug. The stronger the relationship, the more likely the patient will continue problematic use despite internal and external consequences.

As with many drugs, cannabis can enhance or attenuate the effects of other medications. A combination of dronabinol (a cannabinoid) and prochlorperazine is more effective in reducing chemotherapy-associated nausea and vomiting than prochlorperazine alone [130]. Cannabis can also augment the sedating effects of other psychotropic substances, such as alcohol and benzodiazepines. A number of synergistic effects may be therapeutically desirable, such as the enhancement of:

- Muscle relaxants, bronchodilators, and antiglaucoma medication
- Opioid analgesia
- Phenothiazines' antiemetic effect
- Benzodiazepines' antiepileptic action

The cyclooxygenase inhibitors, indomethacin, acetylsalicylic acid, and other NSAIDs antagonize THC effects, reflecting the involvement of cyclooxygenase activity in several THC effects [131].

Cannabis should not be considered as a safe alternative to tobacco products, as it contains many of the same carcinogens as tobacco products [132]. There is some evidence that frequent and/or heavy cannabis use may promote oral cancer development [135]. While there are no oral manifestations specific to prolonged cannabis use, smoking and/or chewing cannabis can cause an alteration in the oral epithelium known as cannabis stomatitis, which is characterized by chronic inflammation of the oral mucosa with hyperkeratosis and leukoplakia. Compared with the general population, chronic cannabis smokers have poorer oral health, more decayed teeth, more plaque accumulation, and poorer gingival health [133].

Aside from the direct effects of cannabis on the oral tissues, the appetite stimulant effects of THC can result in the consumption of cariogenic snack foods. The caries pattern among these patients typically involves the smooth outer or inner surfaces of the teeth [134].

Some habitual cannabis users experience a decrease in salivary flow and in the pH of the oral environment [136]. As discussed, xerostomia has a variety of adverse oral effects that should be addressed, if present.

COCAINE USE DISORDER

Stimulant drugs are substances that activate the central nervous system (CNS) and peripheral nervous system. There are two main categories of commonly used illicit stimulants: cocaine and amphetamine and its derivatives and analogs, such as methamphetamine. Cocaine, a tropane alkaloid, is extracted from the leaves of *Erythroxylumcoca* bush, which contain 0.6% to 1.8% of the alkaloid [137; 138; 139].

Cocaine's specific mechanism of action involves increasing the synaptic transmission of dopamine, serotonin, and norepinephrine by interaction with plasma membrane transporters to block presynaptic reuptake. Action involving the dopamine transporter is the most important in producing the reinforcing effects, which lead to dependence [140].

Cocaine can be absorbed through any mucous membrane. Different routes of cocaine delivery into the body produce different patterns and levels of blood cocaine concentration. Intranasally administered (snorted) cocaine is absorbed and distributed into the body gradually, while the onset of effect is rapid when smoked or injected. The effect of cocaine is experienced most rapidly and intensely when smoked, with an onset of effects typically occurring within 8 to 10 seconds; thus, cocaine is most addictive when smoked [140]. Injected cocaine takes twice as long to enter the brain (i.e., 16 to 20 seconds), and snorted cocaine

begins to act in three to five minutes [141]. The lungs are the most rapid and efficient cocaine delivery modality because of the large surface area of absorption and rapidity of arterial circulation to the brain [143; 144].

Peak plasma levels of cocaine occur 20 to 40 minutes following intranasal ingestion, with a typical concentration of 100–500 mcg/L. Toxicity is rarely seen at this dose level. Plasma half-life ranges from 31 to 82 minutes, with a mean of 38 minutes [142].

Subjective and behavioral effects from single- and multiple-dose acute ingestion of cocaine include euphoria, increased heart rate, restlessness, anxiety and panic, delusions, heightened alertness, and insomnia. Over time, chronic users may develop dysphoria, anxiety, restlessness, and paranoia. The risk of toxicity/overdose increases with continued use as well. Withdrawal from cocaine can also have a blend of physical and behavioral symptoms, including fatigue, decreased ability to concentrate, depression, anxiety, cravings, generalized body aches, chills, and tremors [145].

Patients are unlikely to volunteer use of cocaine during a dental appointment. However, if any common signs or symptoms of cocaine use or cocaine withdrawal are observed, clinicians should have an open, nonjudgmental discussion focusing on the patient's well-being. If appropriate, referral information should be provided.

In patients who may be taking cocaine, local anesthetics with a vasoconstrictor (e.g., 1:100,000 epinephrine) should be avoided. Concurrent use within 24 hours of last cocaine dose potentiates the stimulant effects and can lead to a hypertensive crisis, cerebrovascular accident (stroke), or myocardial infarction (heart attack) [61].

Snorting cocaine can lead to necrosis and perforation of the nasal septum and palate; surgical repair of these defects can be very challenging [146]. Possible oral effects of cocaine use include decay, erosion, gingival recession, decreased salivary pH, periodontal disease, and ulcerated and erythematous gingival tissues from intraoral cocaine deposition [147]. Oral and maxillofacial symptoms of cocaine abuse include xerostomia, bruxism, and temporomandibular joint pain [148].

METHAMPHETAMINE USE DISORDER

Like cocaine, methamphetamine is a CNS stimulant and induces temporary improvements in mental acuity and physical function. The widespread use of methamphetamine stems largely from its potential to produce euphoria, reduce fatigue, enhance performance, suppress appetite, and induce weight loss, coupled with multiple interacting social, biologic, cultural, and psychologic factors [149]. Unlike cocaine and heroin, which are plant-derived and whose synthesis is complex, methamphetamine is easily prepared from simple chemical precursors.

Methamphetamine stimulates the release and blocks the presynaptic reuptake of serotonin, dopamine, and norepinephrine [150; 151]. It is metabolized at a much slower rate than some other stimulants, such as cocaine [152]. Methamphetamine is primarily available as [153]:

- "Speed," a low-grade, locally manufactured powder that is snorted or injected
- Pills that are often combined with other drugs, such as ketamine
- "Base" or "paste," an often locally manufactured, glue-like substance
- "Crystal meth" and "ice," which are highly pure, crystalline forms that are smoked or injected

In addition to euphoria, hyperactivity, and energy, other acute effects of methamphetamine use can include increased confidence and self-esteem, grandiosity, feeling of well-being, heightened attentiveness, elevated body temperature, profuse sweating, restlessness, tremors, aggressive behavior, and uncontrollable jaw clenching. Chronic effects can include paranoia, insomnia, psychotic or violent behavior, pronounced fatigue, poor coping abilities, sexual dysfunction, and dermatologic conditions.

E B

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Department of Veterans Affairs, there is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of methamphetamine use disorder.

(https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf. Last accessed February 15, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

"Meth mouth" is widespread among certain populations of methamphetamine users, particularly those incarcerated for methamphetamine-related offenses [43]. "Meth mouth" (dental deterioration) is a constellation of signs and symptoms associated with chronic use of methamphetamine and is caused by methamphetamine-induced vasoconstriction and reduced salivary flow, methamphetamine-induced vomiting, jaw clenching, the high intake of sugary beverages often seen with methamphetamine users, and abandonment of oral hygiene. This condition is characterized by widespread tooth decay and tooth loss, advanced tooth wear and fracture, and oral soft tissue inflammation and breakdown [43].

The American Dental Association recommends that practitioners be particularly aware of the following signs, which may indicate that dental deterioration is linked to methamphetamine use [44]:

- Unaccounted for and accelerated decay in adolescents and young adults

- Distinctive pattern of decay on the buccal smooth surface of the teeth and the interproximal surfaces of the anterior teeth

- Malnourished appearance of heavy users

The acute effects of methamphetamine can include irritability, agitation, hypervigilance, and possibly violent outbursts, and chronic use of methamphetamine has a greater association with violent behavior than any other psychoactive drug [81]. Users of methamphetamine are also at high risk for being recipients of violence. As such, they may present with dental or oral trauma, the healing of which can be complicated by the oral effects of the drug. As always, dental clinicians and staff should take steps to ensure their own safety and the safety of all of their patients, and protocols should be in place to manage patients who appear agitated or disturbed.

CONCLUSION

The human mind is complex, and there are many forms of mental illness that affect millions of people in the United States and throughout the world. While strides have been made awareness and treatment of mental illness, stigma and lack of social acceptance remain. Aside from the fact that these conditions are medical illnesses that should be considered in any patient, they can also have systemic and oral effects that specifically impact the provision of dental care. As such, it is incumbent to include discussion and documentation of patients' mental illness and related pharmacotherapy as a part of their medical history.

If serious mental illness is present, the patient's physician and/or psychiatrist should be consulted. A collaborative effort by the entire interprofessional team in the treatment of patients with mental illness ensure that patients are able to maintain optimal oral health and a high quality of life.

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