

Drug-Induced Diseases

Section IV: Drug-Induced Psychiatric Diseases

Chapter 18: Depression

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Depression is one of the most common psychiatric illnesses, and it may interfere significantly with a patient's daily functioning and quality of life. Untreated depression is associated with substantial morbidity and increases the risk of suicide and death. An estimated 15% of mood disorders end in suicide.¹ Depression is a biologic illness with an unknown cause. Depression occurring secondary to medications is similar in presentation to endogenous depression and carries similar risks of morbidity and mortality. While the overall prevalence is unknown, drug-induced depression poses a significant challenge for practitioners, as it may undermine the effectiveness of much-needed treatment. The risk of treatment-emergent suicidality (e.g., suicidal ideation and behavior) has more recently been characterized independently, although it often occurs with mood changes and poses significant risks to the patient.

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CAUSATIVE AGENTS

Depression has been associated with many drugs, including antiinfective agents, cardiovascular agents, central nervous system (CNS) drugs, dermatologic agents, hormonal treatments, and immunologic and chemotherapeutic drugs. The *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)*¹ defines substance-induced depression as a prominent and persistent disturbance of mood that occurs during use of a

medication causally related to depression, or within 1 month of intoxication or withdrawal of therapy with a medication. Symptoms must be severe enough to result in clinically significant distress in social, occupational, or other areas of functioning. The clinical features of substance-induced depression may be similar to those of major depressive disorder (MDD), but do not have to meet full diagnostic criteria. In the evaluative literature, depression may be characterized as a specific symptom (i.e., depressed mood), or a cluster of depressive symptoms, or as a diagnostic entity (MDD), though the latter is less common. For the purposes of this chapter, depression is defined as the presence of any one of these three characterizations severe enough to cause a disruption in daily function. Suicide and suicidality are often associated with depression. Suicidality associated with antidepressants, antipsychotics, and anticonvulsants is defined as suicidal thoughts or behaviors or suicide.

All drugs associated with inducing depression for which evaluative support is available in the literature are reviewed in this chapter. The literature supporting an association of drugs with depression is largely comprised of case reports, postmarketing surveillance and retrospective observational studies, making the case for causality difficult. There are few prospective, controlled trials with objective assessments of depressive symptoms or diagnostic criteria. When available, these data are discussed for each agent. A list of drugs that have been associated with depression and the estimated incidence for each agent are presented in Table 18–1.²⁻¹²⁰

Table 18-1. Agents Implicated in Drug-Induced Depression		
Drug	Incidence	Level of Evidence
ANTIVIRAL AGENTS		
Efavirenz ²⁹	1.6-2.0%	A
CARDIOVASCULAR AGENTS		
Clonidine ¹⁵	1.5%	C
Guanethidine ¹⁰⁻¹³	1.5%	C
Methyldopa	3.6%	B
Reserpine ¹⁴	7%	B
RETINOIC ACID DERIVATIVES		
Isotretinoin ²⁻⁹	1–5.5%	B
ANTIDEPRESSANTS^{120,a}		
ANTICONVULSANTS^{57,58}		
Levetiracetam ⁶⁵⁻⁶⁷	4%	A
Phenobarbital ⁶⁰	40%	B
Primadone ⁶¹	70%	B
Phenytoin ^{62,63}	NK	C
Tiagabine ⁶³	3%	A
Topiramate ⁶⁴	5–10%	A
Vigabatrin ⁶⁸	12.1%	A
ANTIMIGRAINE AGENTS		
Triptans ⁷⁶	23.2%	B
ANTIPSYCHOTICS^{120,a}		
Aripiprazole	NK	C
Quetiapine	NK	C
HORMONAL AGENTS		
Corticosteroids ⁴⁷⁻⁵²	1.3–18%	B
Oral contraceptives ^{45,46}	NK	B
GnRH agonists ³³⁻³⁸	26–54%	B
Tamoxifen ³⁹⁻⁴⁴	1–20%	A

SMOKING CESSATION AGENTS		
Varenicline ^{117,118}	NK	B
IMMUNOLOGIC AGENTS		
Interferon- α ^{79-86,98-100}	13–33%	A
Interferon- β ⁸⁷⁻⁹⁷	0–33%	A
GnRH = gonadotropin-releasing hormone; NK = not known.		
^a Refers to risk of suicidal ideation when used as antidepressant.		
Levels of Evidence Designation Description		
A There is evidence of causality from one or more randomized, controlled clinical trials.		
B There is evidence of causality from nonrandomized clinical trials, prospective observational studies, cohort studies, retrospective studies, case-control studies, meta-analyses, and/or postmarketing surveillance studies.		
C There is evidence of causality from one or more published case reports or case series.		

EPIDEMIOLOGY

The estimated lifetime prevalence of depression in the general population is approximately 17%. Depression occurs at a much higher rate in patients with chronic illnesses, such as diabetes and cardiovascular disease.¹²¹ While many drugs have been associated with depression, few have been adequately studied to identify the risk that they impart above and beyond that normally present in the population of patients with disease.

Several literature sources suggest a possible causal association between isotretinoin and depression. There has been a relatively large number of reports of serious depression (37 cases of suicide and 394 cases of depression between 1982 and 2000) associated with isotretinoin submitted to the Food and Drug Administration (FDA). These reports have documented a temporal relationship between use of the drug and onset or worsening of depression. In addition, cases of positive dechallenge with discontinuation of isotretinoin therapy and initiation of psychiatric treatment and positive rechallenge have been reported.³⁻⁵ A retrospective case-crossover study assessing the risk of depression in patients treated with isotretinoin in Quebec revealed a relative risk of 2.68 (95% confidence interval [CI], 1.10–6.48).⁶ Another retrospective study from Saskatchewan and the United Kingdom (U.K.) compared patients treated with isotretinoin to those treated with antibiotics for acne.⁷ There was no increased risk of depression or suicide in patients treated with isotretinoin. A prospective, case-control study compared 100 subjects treated with isotretinoin to 100 subjects treated with topical cream or oral antibiotics.⁸ This study used two depression scales and collected information on the severity of acne, social support, stress, and family history as potential confounders. Depression developed in two patients treated with isotretinoin, but the overall difference between the two groups was not statistically significant.⁸ Another prospective study administered depression inventories to 33 subjects at various times during isotretinoin treatment. In this study, patients' depression scores improved as their acne improved, although improvements were not statistically significant.⁹ Despite the lack of consensus in the literature, many health care providers prescribe isotretinoin with caution and consider depression a substantial risk associated with this drug.

Antihypertensive agents, including angiotensin-converting enzyme (ACE) inhibitors, β -blockers, calcium-channel blockers, anti-adrenergic agents (e.g., reserpine, methyldopa, guanethidine, and clonidine), and thiazide diuretics have been implicated in causing depression in case reports. With the exception of anti-adrenergic agents and β -blockers, little empirical evidence exists to support this association. Reserpine, methyldopa, and guanethidine increase

patients' risk of depression, but these agents are no longer commonly used.¹⁰⁻¹⁴ The association between clonidine and depression is supported by case-report data. However, larger evaluative studies suggest that the incidence of depression in patients taking clonidine is similar to that in the general population.¹⁵ The risk of depression associated with β -blocker therapy remains somewhat controversial. In addition to case reports, two epidemiologic studies support an association with depression, but this association was not confirmed in two prospective studies.¹⁶⁻¹⁹ It has been suggested that true depressive disorders rarely develop in patients treated with β -blockers, but that these patients experience typical β -blocker adverse effects, which leads to misdiagnosis of depression. Studies that have incorporated diagnostic criteria for depressive disorders have failed to identify an association between β -blockers and depression.^{20,21}

Digoxin also has been associated with depression in case reports and two small prospective studies.²¹⁻²³ In a community sample, Palinkas reported that elderly women taking digoxin had higher rates of significant depressive symptoms than women not taking digoxin (10.5% vs. 6.5%), although this difference was not statistically significant.²² In a second study, digoxin exposure was associated with an increased risk of depression in patients with a history of myocardial infarction.²⁰ Psychiatric adverse effects have been reported in association with most antibiotics, but are still considered relatively rare events.²¹ Depression has been observed in patients taking fluoroquinolones and the antitubercular agents cycloserine and ethionamide.²⁵⁻²⁷ These data, however, are limited to case reports, and the overall prevalence is unknown.

Both non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors have been associated with depression. The NNRTI efavirenz appears to confer the greatest risk. In over 1,000 patients treated with efavirenz in clinical trials for an average of 1.6 years, severe depression was reported with an incidence of 1.6%, and suicidal ideation occurred in 0.6% of patients.²⁸ The risk of depression and suicidal ideation increased to 2% in patients with a history of psychiatric disorders. In contrast, a 48-week randomized, controlled trial of patients receiving a protease inhibitor-containing regimen or efavirenz-containing once-daily regimen failed to find a difference in the risk of depression during maintenance treatment.²⁹ In addition, nevirapine, abacavir, and indinavir have been noted in clinical case reports to cause depression.³⁰⁻³²

The prevalence of drug-induced depression associated with hormonal agents ranges from 1% to 54%. Agents that affect sex-hormone production appear to be associated with significant risks for inducing depression. Gonadotropin-releasing hormone (GnRH) agonists induce a profoundly hypoestrogenic state and are associated with significant depressive symptoms in approximately 50% of patients.³³⁻³⁷ Tamoxifen, an antiestrogenic agent, does not appear to confer the same risk. Depression as an adverse effect of tamoxifen was not supported by early placebo-controlled trials in patients with breast cancer.³⁹ However, several published reports suggest that depression may occur in up to 15% to 20% of tamoxifen-treated patients with breast cancer and that it is often overlooked or erroneously attributed to the illness.⁴⁰⁻⁴² These reports do not control for confounding factors, such as the effects of the illness, diagnosis, or adverse effects of chemotherapy, and may overestimate the incidence of tamoxifen-induced depression. The Breast Cancer Prevention (P-1) Study of the National Surgical Adjuvant Breast and Bowel Project provided additional controlled data regarding the association between tamoxifen and depression.⁴³ The P-1 study was a multicenter randomized, double-blind, placebo-controlled chemoprevention trial in which a total of 11,064 women were assigned to receive tamoxifen or placebo for 5 years. The frequency of depression, as assessed by the Center for Epidemiological Studies–Depression was similar in both groups during the first 36 months of the trial.⁴³ However, the presence of risk factors at baseline including history of depression, current or previous

treatment with an antidepressant, or extended periods of dysphoric mood (≥ 12 months) was associated with significant depressive symptoms regardless of treatment arm.⁴⁴

Although depression is the most commonly cited reason for discontinuing therapy with oral contraceptives (OCs), the literature does not contain overwhelming evidence of significant OC-induced depression.⁴⁵ The Royal College of General Practitioners' Oral Contraception Study reported that depression occurred at a rate of 70 per 1,000 person-years in women taking OCs. This is similar to the expected rate of affective disorders in females in the United States (U.S.)-based Epidemiologic Catchment Area studies.¹²² Moreover, the rate of depression in women receiving low-dose estrogen (≤ 35 mcg) was similar to that observed in the control group, suggesting that commonly used low-dose preparations do not carry an increased risk of depression. More recent evaluations have focused on affective changes rather than on identifying a depressive syndrome or disorder. Oinonen and Mazmanian reviewed 13 controlled, prospective studies evaluating affective changes during OC treatment and concluded that women taking OCs have less variability in affect across the menstrual cycle and experience less negative affect during the time of menstruation.⁴⁶

Drugs that affect the hypothalamic–pituitary–adrenal (HPA) axis are associated with depression. Corticosteroids have been associated with significant psychiatric adverse effects, including depression, mania, and psychosis.⁴⁷ The occurrence of severe depression in patients taking corticosteroids is supported by case reports.^{48,49} Data from case series, observational studies, and controlled trials also support an association with depression. However, many of these reports fail to quantify the prevalence of significant depressive symptoms.^{47,50,51} The largest observational study, the Boston Collaborative Drug Surveillance Program, found that severe psychiatric symptoms, including depression, were relatively uncommon (1.3%) in patients without a psychiatric history who were taking low doses of corticosteroids (< 40 mg/day prednisone equivalents).⁵² However, the incidence increased to 18% in patients taking > 80 mg/day prednisone equivalents. A cross-sectional study comparing self-reported depression in steroid-using and non-steroid-using patients with chronic obstructive pulmonary disease reported significantly higher depression scores in the steroid-using group.⁵⁰ Furthermore, in a short-term prospective cohort study of medical inpatients, corticosteroid exposure was associated with a threefold increased risk of incident depressive symptoms.⁵³

Several CNS-acting drugs have been associated with depression, including anti-epileptic drugs (AEDs), benzodiazepines, physostigmine, and 5-hydroxytryptophan (HT)₁ agonists (triptans). The AEDs levetiracetam, phenobarbital, primidone, phenytoin, tiagabine, topiramate, and vigabatrin have been reported to cause depression. Conversely, many of the AEDs may be used to stabilize patients with mood disorders. Sodium valproate, carbamazepine and lamotrigine have FDA-approved indications for bipolar disorder. In addition, several AEDs including phenytoin and carbamazepine have demonstrated effectiveness in the management of unipolar depression.^{54,55} It is important to note that, because of ethical considerations, very few of the AED epilepsy trials are strictly placebo-controlled. Because of the various CNS activities of the AEDs used as comparators, it is difficult to judge the exact prevalence of depression caused by these agents. Also, the rate of depression in patients with epilepsy is very high (32–48%) and the lifetime prevalence of suicide and suicide attempts is 5% to 14% in this population.⁵⁶ Therefore, this increase in the incidence of mood disorders can be only partially attributed to the AEDs. All of the AEDs, particularly at higher doses, are associated with lethargy, fatigue, drowsiness, and asthenia, which may mimic depression. In January 2008, the FDA issued an alert regarding suicidality related to AEDs.⁵⁷ Data from 199 placebo-controlled trials of 11 AEDs

(carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, zonisamide) were analyzed, and the investigators reported suicidal ideation or behavior in 0.43% of patients taking AEDs as compared with 0.22% of those taking placebo. The relative risk of suicidal behavior or ideation in patients taking AEDs for epilepsy was 3.53 (95% CI, 1.28–12.1) as compared with 1.51 (95% CI, 0.95–2.45) for those taking AEDs for psychiatric reasons and 1.87 (95% CI, 0.81–4.76) for those taking AEDs for other reasons.⁵⁷ No specific AED or demographic group appeared to be at greater risk.

Of the AEDs, the barbiturates are most strongly associated with depression in both adult and pediatric populations.⁵⁸⁻⁶¹ In one cross-sectional sample of adult patients in Mexico City, primidone use was strongly associated with depression, with an odds ratio of 4.089 (95% CI, 2.094–7.985). In this sample, 70% of the patients treated with primidone were depressed.⁶¹ In another study, phenobarbital was associated with an incidence of depression of 40%.⁶⁰ Data relating phenytoin use to depression are much less convincing. There are case reports of two patients with epilepsy who had supratherapeutic serum phenytoin concentrations (22.7 mcg/mL and 25.5 mcg/mL) who also had depressive symptoms. When the phenytoin dose was decreased or the medication was discontinued, the symptoms resolved.⁶² A prospective study of 277 subjects in whom tiagabine or placebo was added to baseline AED therapy found depression in 3% of those treated with tiagabine.⁶³ Topiramate treatment has been associated with new-onset depression in 5% to 10% of patients.⁶⁴ Depression was reported in 4% of levetiracetam-treated subjects as compared with 2% in those treated with placebo.⁶⁵ A retrospective case series and an additional case report have also implicated levetiracetam as a cause of depression.^{66,67} Vigabatrin-associated depression occurred in 12.1% of patients treated in doubleblind, placebo-controlled clinical trials ($P < 0.001$).⁶⁸

Depression often is cited as an adverse effect of benzodiazepines, both during therapy and after discontinuation.⁶⁹ However, the literature supporting incident depression in patients taking benzodiazepines is not robust, and depression is reported infrequently in controlled clinical trials. Case reports and observational studies have identified an increased risk of depression in patients taking benzodiazepines.⁷⁰⁻⁷³ These reports, however, do not control for confounding variables, such as history of depression, presence of comorbid depression, or concomitant medications, and are therefore difficult to interpret. Depression and anxiety are highly comorbid syndromes, and the emergence of depression during benzodiazepine therapy may occur from a relapse or as a coincidental finding. Moreover, alprazolam administered in higher doses has been shown to have an antidepressant effect.⁷⁴

Physostigmine was associated with immediate depressive symptoms in nine normal volunteers administered high intravenous doses.⁷⁵ Whether the results of this study apply to patients with myasthenia gravis who take oral physostigmine, with relatively low bioavailability, is unknown.

Only a single epidemiologic study exists to implicate triptans as causative agents for depression. A cohort analysis of the West Midlands General Practice Research Database in the U.K. examined the incidence of depression in migraineurs receiving any oral triptan, sumatriptan, or the more lipophilic medications (naratriptan or zolmitriptan).⁷⁶ A larger proportion of the 1,062 patients (23.2%) receiving any oral triptan were diagnosed with depression, as compared with 16.8% of 18,033 patients not receiving an oral triptan ($P < 0.001$). When specific medications were compared, no difference in the number of patients diagnosed with depression after their first prescription was found between those receiving sumatriptan (4.2%) and those receiving naratriptan or zolmitriptan (3.9%) ($P = 0.87$).

Several medications used in immunotherapy and chemotherapy, including interferon- α , interferon- β , and interleukin (IL)-2 have demonstrated associations with depression. In addition, the immunosuppressant agent mycophenolate was reported to cause depression in a patient using the drug for myasthenia gravis.⁷⁷ Multiple types of α interferons (INF α) are available: recombinant INF α 2a; recombinant INF α 2b; INF α n3, a mixture of at least 15 different interferon subtypes produced from human leukocytes; peginterferon α 2a, a combination of recombinant INF α 2a and an inert 40kD polyethylene glycol polymer; peginterferon α 2b, a combination of recombinant INF α 2b and an inert 12-kD polyethylene glycol polymer; and INF alfacon-1 (consensus INF), a recombinant, synthetic product. Depression has been reported in association with each type of INF α .⁷⁸⁻⁸⁶ Several trials investigating the relationship of depression and the various INF α s have been conducted, with treatment-emergent depression reported in 16% to 96%⁷⁸⁻⁸⁰ of patients. Although none of these trials were placebo-controlled, many used standardized instruments to assess depression. One study examined the effect of INF α over time and found decreased numbers of patients with depression after 6 months of therapy (8–33%) as compared with 1 month (79–96%; $P = 0.03$).⁸⁰

Two β interferons are available in the U.S. for treatment of multiple sclerosis (MS). Interferon-beta (INF β) 1a is available for intramuscular or subcutaneous injection and INF β 1b is administered subcutaneously. The data regarding INF β -precipitated depression are less clear than those for depression induced by INF α . Two controlled trials suggest an increased risk of depression associated with INF β 1a, with incidences ranging from 20% to 33%.^{105,106} Two other studies of INF β 1a have not revealed an increased prevalence of depression as compared with that associated with placebo.^{107,108} Only one trial compared the two commercially available formulations of INF β 1a. The Evidence for Interferon Dose-Effect: European-North American Comparative Efficacy (EVIDENCE) study assigned 677 subjects to receive either INF β 1a 44 mcg subcutaneously three times weekly or INF β 1a 30 mcg intramuscularly weekly for 24 weeks.⁹¹ No difference in depression between the two treatment groups was reported (17% vs. 18%).

A long-term seminal trial of INF β 1b demonstrated higher rates of depression with the clinically-used 8 MU dose compared with those associated with placebo at each yearly timepoint.⁹² Two trials have been conducted to specifically examine rates of depression associated with INF β 1b. One study reported depression in a mean (\pm SD) 13 \pm 4% of patients, though no formal testing for depression was performed.⁹³ Another small study found a decreasing rate of reported depression over the 1-year study period, ranging from 21.4% of subjects at baseline to 6.3% of subjects at 12 months.⁹⁴ Only one study comparing two of the INF β products examined depressive symptoms. The Independent Comparison of Interferon (INCOMIN) trial noted depression in 22% of subjects (18 of 88) given INF β 1a 30 mcg intramuscularly weekly and in 19% of subjects (18 of 94) given INF β 1b 8 mcg subcutaneously every other day ($P = 0.68$).⁹⁵ A prospective cohort of 182 patients started on any INF β treatment were administered the Hamilton Rating Scale for Depression and the Beck Depression Inventory at baseline and after a mean treatment duration of 65.6 months. There was no increase in the number of patients demonstrating depression over this time.⁹⁶ A Canadian database analysis of antidepressant prescription claims for patients with multiple sclerosis failed to detect a significant difference in the percentage of patients receiving antidepressant prescriptions between INF-treated and glatiramer acetate-treated patients. However, the percentage of patients in all cohorts receiving antidepressant medications was high (40%).⁹⁷

IL-2 also has been reported to cause depression. In two studies of patients with metastatic carcinoma, patients administered IL-2 were found to be significantly more likely to have depression than those not receiving IL-2 therapy.^{98,99} The association between other chemotherapeutic agents and depression is more tenuous. One trial examined two regimens for the treatment of small-cell carcinoma of the lung in 77 patients.¹⁰⁰ Regimen 1 consisted of methotrexate, doxorubicin, lomustine, and cyclophosphamide. Regimen 2 comprised cyclophosphamide, doxorubicin, vincristine, and lomustine. Subjects were tested with the Profile of Mood States at baseline and after completion of therapy. Increased depression ratings following therapy were reported in 30% (not statistically significant as compared with baseline) of those receiving regimen 1 and 48% ($P = 0.03$ as compared with baseline) of those receiving regimen 2. The authors speculated that the larger proportion of patients with increased depression rating scores in patients who received regimen 2 can be attributed to vincristine. A case report also implicates vincristine as a cause of depression.¹⁰¹ A patient treated for acute myoblastic leukemia who received vincristine 10 mg instead of 1 mg had severe depression with uncontrollable crying. The symptoms dissipated over a 3-week period.

Other drugs that have been implicated in depression in case reports include 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, histamine₂-receptor blockers, amiodarone, nonsteroidal antiinflammatory drugs, metoclopramide, ondansetron, and psychostimulants.¹⁰²⁻¹¹⁶ However, cause-effect relationships have not been established for any of these agents. Similarly, postmarketing adverse event reporting largely from case reports identified a risk of neuropsychiatric adverse events including depression and suicidality associated with the nicotine-receptor agonist varenicline and the leukotriene antagonist montelukast. These reports prompted the FDA to require stronger warning language in the product information.¹¹⁷⁻¹¹⁹ In placebo-controlled trials of 4,400 patients, varenicline was associated with higher risk of depression than no treatment. However, patients with a history of psychiatric disorders were excluded from these trials. Postmarketing surveillance revealed severe neuropsychiatric events, including suicide, occurring during and after treatment with varenicline. While smoking cessation may be associated with nicotine withdrawal symptoms including depression and agitation, there appears to be an increased risk of these symptoms associated with varenicline, as some of these cases occurred while patients were still smoking.^{117,118}

Antidepressant medications would not be expected to cause drug-induced depression. However, antidepressant drugs are associated with an increased risk of suicidality in patients younger than 25 years of age.¹²⁰ Pooled analyses of 24 short-term placebo-controlled antidepressant trials in over 4,400 children and adolescents with MDD, obsessive-compulsive disorder, or other psychiatric disorders showed that these drugs increased the risk of suicidality, although no suicides were reported. Antidepressant treatment in patients younger than 18 years of age resulted in an additional 14 cases of suicidality per 1,000 patients treated. The pooled analyses of 295 short-term placebo-controlled studies in over 77,000 adults aged 18 to 24 years with MDD or other psychiatric disorders showed an additional 5 cases of suicidality per 1,000 patients treated. There was no increased risk in adults aged 25 to 64 years, and there was a reduced risk in adults ≥ 65 years (6 fewer cases per 1,000 patients). All antidepressant medications, including antipsychotics with an FDA indication for MDD (e.g., aripiprazole and quetiapine), have a boxed warning for suicidality in the product information. This risk should be carefully considered when choosing a treatment intervention for MDD.

MECHANISMS

Drug-induced depression occurs through several mechanisms, including direct alteration of bioamine function, disturbance of HPA axis function, dramatic hormonal changes, and elevation of cytokine production (Table 18–2).

TABLE 18–2. Mechanisms of Drug-Induced Depression

Drug	Mechanism
Reserpine	Depletes neuronal norepinephrine, serotonin, and dopamine
Guanethidine	Depletes neuronal norepinephrine
Methyldopa	Partial agonism of norepinephrine receptor
Clonidine	Reduces norepinephrine output via α_2 -adrenergic receptor agonism
Digitalis	Inhibits central nervous system synthesis of norepinephrine
Isotretinoin	Alters dopaminergic, serotonin, and possibly norepinephrine systems
Leuprolide	Reduces both estrogen and androgen production
Tamoxifen	Reduces estrogen function via antagonizing estrogen receptors
Cortisone	Elevates plasma cortisol concentrations
Phenobarbital	Reduces plasma unbound tryptophan, which influences plasma serotonin concentrations
Topiramate	Increases the amount of GABA available
Tiagabine	Increases the amount of GABA available
INF α	Increases interleukin-6 production
Vincristine	Prevents the conversion of dopamine to norepinephrine
Varenicline	$\alpha_4\beta_2$ -nicotinic receptor agonist, indirectly modulates dopamine

GABA = γ -aminobutyric acid.

The antihypertensive agents reserpine, guanethidine, and methyldopa all likely induce depression by depleting CNS bioamine activity.¹²³ Guanethidine and reserpine deplete norepinephrine at the synapse. Methyldopa is transformed into α -methyl norepinephrine, which is less active than norepinephrine and replaces it at the sympathetic nerve endings, thus acting as a false neurotransmitter. Notably, the norepinephrine depletion caused by reserpine generated one of the early theories of the pathogenesis of depression (e.g., the monoamine hypothesis).^{124,125} Clonidine also reduces central norepinephrine output via stimulation of α_2 -adrenergic receptors.¹²⁶

β -blockers exert a specific centrally-mediated effect on both β -adrenergic and serotonin receptors. Chronic β -receptor blockade results in increased β -receptor binding, an effect opposite to that associated with antidepressants. This reduces β -receptor binding and receptor density.^{127,128}

The mechanism of digoxin-induced depression is unknown, although alteration of CNS norepinephrine synthesis is suspected. In animal models, digitalis has been shown to inhibit CNS synthesis of norepinephrine and to decrease norepinephrine uptake by CNS tissue, with an apparent overall activation of CNS noradrenergic function. Altered activity of CNS dopaminergic and serotonergic systems also has been demonstrated, particularly with high digitalis doses.²⁴ Similarly, the mechanism of isotretinoin-induced depression is not clear, but animal studies suggest alterations in the dopaminergic, serotonin, and possibly norepinephrine systems.¹²⁹

GnRH agonists induce a hypogonadal state, resulting in a significant reduction in both estrogen and androgen production. Significant fluctuation in serum estrogen concentrations and low estrogenic states have been associated with substantial mood symptoms in patients with

premenstrual dysphoric disorder and during menopause. The significant decline in estrogen production associated with GnRH agonist therapy is believed to be the cause of depressive symptoms in these patients. Estrogen may affect mood in several ways, such as by increasing the availability of neurotransmitters, including serotonin, by enhancing the degradation of monoamine oxidase.¹³⁰ Estrogen modulates serotonin in other ways, including regulation of tryptophan, a serotonin precursor, and increasing the number of serotonin transport sites.¹³¹ Tamoxifen, an estradiol receptor antagonist, also may produce depressive symptoms caused by a decline in estrogen function. However, raloxifene, a selective estradiol receptor antagonist, without CNS activity, does not appear to induce depression.¹³²

A number of mechanisms have been proposed regarding the mood effects of OCs. Estrogen may induce a pyridoxine deficiency resulting in a decrease in serotonin and γ -aminobutyric acid (GABA) concentrations in the CNS. Vitamin B₆ has been suggested as an effective treatment.¹³³ Other possible mechanisms include an estrogen- and progesterone-mediated augmentation of GABA's inhibition and suppression of glutamate and a progesterone-mediated increase in monoamine oxidase activity.^{130,134}

Corticosteroids are thought to induce mood symptoms by elevating plasma cortisol concentrations. Patients with Cushing's disease have been reported to have high rates of depressive symptoms.¹³⁵ Moreover, abnormalities of the HPA axis with hypercortisolemia are found in patients with MDD.¹³⁶ It is of interest that corticosteroids are as likely to induce mania as depression, suggesting a complex interaction.⁴⁸

The mechanism of AED-induced depression likely involves GABA, an inhibitory neurotransmitter, alterations in serotonin activity or a combination of these. Some evidence suggests that antidepressant agents enhance activity at GABA-B receptors and decrease activity at GABA-A receptors.¹³⁷ Therefore, agents that primarily act at the GABA-A receptors, such as phenobarbital, tiagabine, or topiramate, or indiscriminately increase the amount of GABA available to both receptors, such as tiagabine, may be associated with greater potential for inducing depression. Both phenobarbital and phenytoin reduce unbound plasma tryptophan concentrations, which influences serotonin turnover.¹³⁸ In addition, the enzyme-inducing AEDs can cause a folate deficiency. Decreases in plasma folate concentrations may reduce methylation reactions involving neurotransmitters and monoamines, which may be implicated in depression induction.¹³⁹

The mechanisms of depression caused by the immunologic agents have not been elucidated completely. Most work in this area has been conducted with $\text{INF}\alpha$, and several mechanisms have been proposed that may be applicable to $\text{INF}\beta$ and IL-2. $\text{INF}\alpha$ induces the production of proinflammatory cytokines, such as IL-6, which may lead to depression.⁸¹ An increase in the Montgomery-Asberg Depression Rating Scale scores was significantly and positively correlated with increases in serum IL-6 concentrations.⁷⁰ $\text{INF}\alpha$ affects the serotonergic system to increase serotonin transporter messenger ribonucleic acid and uptake activity, suppress serotonin concentrations in brain or serum, and induce the catabolism of tryptophan.⁸¹ The net effect of these alterations in the serotonin system is to decrease the amount of serotonin at the active receptor sites and potentiate depression. $\text{INF}\alpha$ administration is also associated with activation of the HPA,⁸¹ which has been associated with depression and with increases in serum IL-6 concentrations.^{140,141} A depletion of tryptophan, the amino acid precursor to serotonin, caused by $\text{INF}\alpha$ administration has also been hypothesized.¹⁴² A polymorphism (C1019G) on the allele coding for the 5-HT_{1A} receptor (HTR1A) has also been implicated in the development of $\text{INF}\alpha$ -induced depression. The HTR1A receptor is the major autoreceptor on the serotonergic

raphe neurons. Alterations in this receptor can lead to decreased secretion of serotonin. This polymorphism is relatively common, with approximately 48% of people having at least one C1019G allele. This finding may help explain the very common occurrence of depression in patients treated with $\text{INF}\alpha$.¹⁴²

Vinca alkaloids have been shown to inhibit the transport of dopamine hydroxylase, thereby preventing the conversion of dopamine to norepinephrine,¹⁰¹ the resultant effect of which could be depression. The mechanism of varenicline-induced depression is unknown, but the partial $\alpha_4\beta_2$ -nicotinic receptor agonist indirectly modulates dopamine,¹⁴³ which may in turn modulate mood.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Drug- or substance-induced depression is defined by DSM-IV as a prominent and persistent disturbance of mood that occurs during use or within 1 month of intoxication or withdrawal of therapy with a medication.¹ The key feature of diagnosis is the temporal association between the development of depressive symptoms and the use of a causative drug. The disturbance of mood or presence of depression should be severe enough to result in impairment of daily function. In addition, the clinician must rule out the possibility of preexisting depression and the influence of the disease state being treated, particularly psychological stressors.

Symptoms associated with drug-induced depression (Table 18–3) are similar to those observed in patients with MDD, with few exceptions. More severe symptoms including suicidal ideation and psychotic symptoms have been reported in association with $\text{INF}\alpha$, corticosteroids, and varenicline.^{48,52,82,117,118} With most agents, the onset of depression generally occurs during the first weeks of treatment. The median onset of symptoms in FDA-reported cases of isotretinoin-associated depression during the first course of therapy was 30 days, and the median recovery time was 4.5 days.⁵ During the rechallenge course, the time to onset of symptoms was shorter.¹⁴⁴ Patients treated with GnRH agonists have depressive symptoms that are consistent with the time to reach a hypogonadal state.^{33,34} When the hypogonadal state is of short duration, as with in vitro fertilization treatment, depressive symptoms are transient and less severe.³⁸ However, during sustained treatment for endometriosis, depressive symptoms appear to be persistent and generally more severe, sometimes resulting in the need for discontinuation of treatment.^{35,39,145} Drug-induced suicidality is temporally associated with initiation of treatment and represents a marked change in thoughts and behavior from baseline.¹²⁰ Suicidality associated with anticonvulsants and antidepressants occurs early in treatment, and must be distinguished from the underlying mood disorder for which they have been prescribed.

TABLE 18–3. Signs and Symptoms Associated with Drug-Induced Depression

- Depressed mood
- Diminished interest or pleasure in most activities
- Sleep changes (insomnia or hypersomnia)
- Appetite increase or decrease
- Hopelessness/helplessness
- Suicidal ideation
- Fatigue

- Decreased concentration
- Psychomotor agitation or retardation

Conditions and diseases associated with depression must be ruled out in order to arrive at a diagnosis of drug-induced depression (Table 18–4). The incidence of depression in patients with epilepsy ranges from 4% to 62%, depending on the method of diagnosis and the population studied.^{146,147} One study found that patients with hypertension were three times more likely to have depression than normotensive patients.¹⁴⁸ Many chronic health conditions for which immunologic agents are used have been associated with high rates of depression. The prevalence of depression in patients with chronic hepatitis C is 11% to 30%,¹⁴⁹ while the prevalence of depression in patients with cancer is 28%.¹⁵⁰ Multiple sclerosis is also associated with a 15% to 30% point prevalence of depression and a lifetime depression incidence of 40% to 60%.¹⁵¹ Fatigue, a symptom common to all of the disease states in this category, often can be confused with depression. Alternatively, depression may be underdiagnosed because of the expectation that patients will present with fatigue. Other conditions that may cause misdiagnosis of depression include hyperthyroidism and hypothyroidism and unrealistic expectations, leading to discouragement and frustration.¹⁵²

TABLE 18–4. Conditions to Consider in the Differential Diagnosis of Drug-Induced Depression

- Substance-use disorder
- Preexisting mood disorder
- General medical conditions
 - Endocrine
 - Infectious
 - Deficiency state
 - Collagen disorders
 - Metabolic disorders
 - Neurologic disorders
 - Cardiovascular disease
 - Malignant disease

RISK FACTORS

Female sex, family history of mood disorder, childhood abuse, anxiety disorders, sleep disorders, and neurologic disorders are known risk factors for MDD.¹ It is unclear, however, whether these factors also increase the risk of drug-induced depression. Much of the literature regarding drug-induced depression arises from case reports, database evaluations, and observational studies, which are not designed to identify risk factors. Factors that appear to increase the risk of drug-induced depression are listed in Table 18–5.

TABLE 18–5. Risk Factors for Drug-Induced Depression

Risk Factors Common to All Drugs

- History of major depressive disorder or prior depression episode
- History of drug-induced depression
- Psychosocial stressors (e.g., financial, relationship, or job stress)

Risk Factors Associated with Specific Drugs

- Corticosteroids

- Dose (>80 mg/day prednisone equivalents)
 - Efavirenz
 - Plasma concentrations >2.74 mcg/L during longterm treatment
 - Topiramate
 - Dose (higher starting dose of 50 mg/day, titration of 50 mg/day every 2 wk)
 - Temporal-lope epilepsy with hippocampal sclerosis
 - Presence of cognitive adverse effects
 - Family history of epilepsy
 - History of febrile seizures
 - Interferon-alfa
 - Homozygous for the HTR1A-1019G allele
 - Increased immune activation (e.g., increased soluble IL-2 receptor, IL-6, and IL-10 serum concentrations) prior to treatment for hepatitis C
 - Oral contraceptives
 - History of premenstrual depression or pregnancyrelated depression
 - History of dysmenorrhea
 - Family history of depression while taking oral contraceptives
 - Predisposition to vitamin B₆ deficiency
 - High degree of psychological distress prior to oralcontraceptive use
 - Age <20 yr experience negative affect more often
 - High estrogen/progesterone content
- IL = interleukin.

A history of depression or another psychiatric disorder is the most consistently identified risk factor for depression associated with most of the causative drugs. In addition, the presence of psychological stressors has been noted to increase the risk. While increased stress may be expected in patients with serious medical illnesses, it is unclear whether increased stress increases the risk of depression associated with drugs such as immunologic or cancer chemotherapeutic agents. Patients with a history of drug-induced depression are likely to be at greater risk upon repeated exposures.¹⁵

Dose may be an important risk factor for depression associated with some agents. Depression is more likely to occur when higher doses of corticosteroids are used (>80 mg/day prednisone equivalents).⁵³ It is unclear whether multiple courses of corticosteroids increase the risk of depression. However, patients with a history of steroid-induced depression should be monitored closely. Likewise, oral contraceptives with higher estrogen content are more commonly associated with depression. Some open-label data suggest that the risk of neuropsychiatric adverse effects associated with long-term treatment (>6 months) with efavirenz were more than five times greater in patients with plasma efavirenz concentrations >2.74 mcg/L.¹⁵³

Several factors have been specifically associated with an increased risk of treatment of emergent depression or negative affect in patients taking OCs (Table 18–5). Whereas the overall risk for depression caused by these drugs is considered low, patients presenting with any of these factors should be considered at greater risk. The risk may vary with the type of OC used. Monophasic OCs exert greater mood-stabilizing effects than triphasic products. In addition, patients with premenstrual mood symptoms may have an increased risk of negative mood effects with OCs containing low amounts of progesterone or a low progesterone-to-estrogen ratio. Women without premenstrual mood symptoms appear to have increased risk with a higher progesterone content.⁴⁷

A retrospective study of patients with temporal lobe epilepsy who were initiated on topiramate therapy revealed that those with hippocampal sclerosis in association with temporal-lobe epilepsy were significantly more likely to have depression than those without hippocampal sclerosis. Patients without hippocampal sclerosis who had cognitive adverse effects such as psychomotor slowing or word-finding difficulties associated with topiramate were also more likely to be diagnosed with depression.¹⁵⁴ A case series of patients started on topiramate therapy found that a higher starting dose (50 mg daily) and a faster titration schedule (increase of 50 mg/day every 2 weeks) as well as the presence of cognitive adverse effects caused by topiramate increased the odds of any psychiatric adverse events, including depression. Other related factors were family or personal history of psychiatric conditions, family history of epilepsy and a history of febrile convulsions.⁶⁴

Risk factors for depression associated with INF α treatment include hepatitis C and an increase in vegetative symptoms of depression on the Zung depression rating scale after 4 weeks of treatment.^{155,156} Patients who were homozygous for the HTR1A-1019G allele had an approximate threefold risk increase of depression induced by INF α treatment.¹⁵⁷ One small study of 16 patients undergoing treatment with various INF α regimens for hepatitis C found that patients with higher levels of immune activation as demonstrated by increased soluble IL-2 receptor, IL-6, and IL-10 serum concentrations prior to treatment were more likely to have major depressive disorder as measured by DMS-IV criteria and the Montgomery–Asberg Depression Rating Scale score.¹⁵⁸

The risk for suicidality associated with antidepressants is inversely related to age, with patients <18 years at greatest risk, and adults 18 to 24 years at greater risk than older adults (25 to 64 years).¹²⁰ Antidepressant selection, dose, or indication do not significantly change the risk of suicidality within the stratified age groups. Conversely, patients receiving an AED for epilepsy are 3.4 times more likely to experience suicidality than patients with psychiatric disorders.

MORBIDITY AND MORTALITY

Drug-induced depression can be associated with significant morbidity and mortality. Many drugs associated with depressive symptoms are used to treat chronic medical disorders or are components of lifesaving or prolonging therapeutic regimens. Patients experiencing significant depressive symptoms as a result of their treatment may be less likely to adhere to therapy and may be less optimistic about potential treatment benefits. Furthermore, the development of severe depressive symptoms may necessitate the discontinuation of lifesaving treatments.

The presence of depression or severe depressive symptoms may increase the risk of suicide or suicidal ideation. Whereas the prevalence of suicide risk in patients with drug-induced depression is unknown, up to 15% of patients with severe MDD die as a result of suicide.¹ Moreover, patients with MDD have decreased physical, social, and role functioning as well as increased pain and physical illness.¹⁵⁹ The risk of suicidality associated with antidepressant treatment must be balanced with the much greater risk of suicidality in patients with untreated depression.

PREVENTION

There is very little information available regarding preventive strategies for drug-induced depression. However, some interventions may prove useful (Table 18–6). Identifying patients with risk factors (e.g., history of depressive episode) and implementing a prospective monitoring plan seems prudent, but will not prevent drug-induced depression. Careful monitoring and early detection may, however, minimize the negative sequelae associated with depression. Treating psychosocial stressors with interventions such as counseling and education may also prove beneficial, but this strategy has not been systematically evaluated. Pretreatment or prophylaxis for depressive symptoms may be useful in some cases. Sabet reported the successful pretreatment (with lithium and protriptyline) of an individual with a history of steroid-induced depression.¹⁶⁰ In a retrospective review of patients receiving leuprolide for treatment of endometriosis, concomitant treatment with sertraline minimized the emergence of depressive symptoms.¹⁵⁸ Convincing evidence exists regarding the benefit of pretreatment for depression in patients with melanoma receiving INF α . Musselman et al.¹⁶¹ randomly assigned 40 patients with melanoma to receive pretreatment with paroxetine (n = 20) or placebo (n = 20) 2 weeks prior to and throughout the 12-week INF α regimen. The risk of developing depression was lower in the paroxetine group (11% vs. 35%; relative risk, 0.24; 95% CI, 0.08–0.93) and pretreated patients were less likely to discontinue INF α because of depressive symptoms (5% vs. 35%; relative risk, 0.14; 95% CI, 0.05–0.85). A small group (n = 10) of patients with hepatitis C who had a history of major depression were administered escitalopram preventively during treatment with peg-INF α 2a and ribavirin. Only one patient from this group had depression (Hamilton Rating Scale for Depression, >17) during the course of 24 to 48 weeks of INF treatment.¹⁶² Amantadine, a medication with both antiviral and dopaminergic effects, was studied in 14 subjects who were treated with peg-INF α 2a and ribavirin for hepatitis C. As compared with the control group, amantadine-treated subjects were significantly less likely to have depression by week 24 of treatment.¹⁶³

TABLE 18–6 Approaches to Help Prevent Drug-Induced Depression

- Assess patient for history of depressive episodes or history of drug-induced depression at baseline
- If Yes:
 - Consider individual risk–benefit of drug therapy
 - Select alternative drug within therapeutic category, if possible
 - Pretreatment with selective serotonin reuptake inhibitor if undergoing therapy with interferon or gonadotropin-releasing hormone agonist

MANAGEMENT

Appropriate management (Table 18–7) of drug-induced depression begins with prompt recognition of the emergence of depressive symptoms. In some cases, depressive symptoms may be transient or mild, as in patients receiving GnRH agonist therapy as part of in vitro fertilization treatment.³⁸ For many patients, education and support may be the only intervention needed. Psychological interventions or psychotherapy prove beneficial for patients with mild-to-moderate symptoms of MDD, but the benefit of psychotherapy in patients with drug-induced depression is unclear. For more severe or persistent depressive symptoms, therapy with the

offending agent will likely have to be discontinued or antidepressant treatment may need to be initiated, and in some cases, both strategies are required. Children, adolescents, and young adults (18–24 years) receiving antidepressants for depression or other psychiatric disorders should be monitored frequently (weekly to biweekly) during the first few weeks for treatment-emergent suicidality or worsening of depression. The emergence of suicidal ideation or psychotic symptoms should always be considered serious, and these patients should receive immediate intervention, including hospitalization.

TABLE 18–7 Management of Drug-Induced Depression

- Discontinue the offending agent, if possible
- Substitute medication within therapeutic class
- Counseling or supportive therapy for mild depressive symptoms
- Initiate antidepressant therapy for persistent or moderate-to-severe depressive symptoms

There are insufficient data to recommend specific doses of antidepressant therapy for the treatment of drug-induced depression, although in most reports doses similar to those used in patients with endogenous depression have been administered. Duration of therapy should be based on patient response and clinical judgment. In cases in which it would be best for a patient to continue to receive therapy with the causative agent, clinicians should consider factors such as severity of presentation, current mood, and level of psychological stress before deciding to discontinue drug therapy.

While not always possible, in some cases substituting another medication in the same drug or therapeutic class but with a lower risk of causing depression may represent the best management strategy. For example, patients experiencing β -blocker-induced depression may benefit from receiving a hydrophilic β -blocker or an antihypertensive drug from a different class (e.g., ACE inhibitor or diuretic).¹⁶⁴ Similarly, patients experiencing OC-induced depression may benefit from an OC with a lower estrogen content or different estrogen:progesterone ratio. Patients with varenicline-induced neuropsychiatric side effects should be considered for nicotine replacement or bupropion for smoking cessation.

No specific treatments have been proposed for depression associated with the immunologic agents. Discontinuation of therapy is sometimes considered, but remission of depression does not always occur simultaneously with the discontinuation of interferon.¹⁴⁷ For patients with hepatitis C, selective serotonin reuptake inhibitors may be the best choice, as they are well tolerated by patients with liver disease, whereas tricyclic antidepressants with significant anticholinergic effects may increase the cognitive dysfunction that occurs in these patients.¹⁴⁷ Gleason et al.¹⁶⁵ conducted a study using citalopram to treat depression in patients with hepatitis C. Of the 15 subjects participating in the trial, four had previously taken INF α and four were currently receiving INF α therapy. Citalopram 10 to 40 mg/day was administered to all subjects, with a resultant improvement in mood. In another study, 13 patients on therapy with INF α had depression, 85% of whom were responsive to treatment with citalopram.¹⁶⁶ Similar results were achieved with citalopram in another study.¹⁵⁷ There are case reports of patients with INF α -induced depression who were responsive to treatment with methylphenidate or venlafaxine.^{167,168}

Selection of specific INF α therapy based on patients' depressive symptoms has been proposed. For patients with suicidal tendencies, INF α n3 is preferred; for patients experiencing depersonalization, INF α 2a is suggested; patients with paranoia may experience fewer symptoms with INF α 2a or INF α 2b; and those patients exhibiting obsessive or compulsive symptoms may improve during treatment with INF α n1.⁸² However, these recommendations are based on

relatively small numbers of individuals and the symptoms expressed by those individuals in a clinical trial, and require evaluation in a prospective trial. Sertraline has proven effective for the management of depressive symptoms associated with GnRH agonists.^{34,35,152} Lithium, selective serotonin reuptake inhibitors, and electroconvulsive therapy have been used to manage steroid-induced depression.⁴⁸

There is inherent difficulty in recommending antidepressant therapy for patients with epilepsy because of the epileptogenic potential of most antidepressant drugs. Bupropion may exert proconvulsant properties in persons without epilepsy, particularly in doses >450 mg/day.¹⁶⁹ Tricyclic antidepressants also may have epileptogenic potential, particularly amoxapine, clomipramine, maprotiline, and mianserin.¹³⁹ Although selective serotonin-reuptake inhibitors are generally preferred in patients with epilepsy, they have been associated with seizures in case reports. This may be caused, in part, by an increased incidence of hyponatremia, which may induce seizures.¹⁷⁰

INFORMATION FOR PATIENTS

Patients should be informed regarding the possibility of the emergence of depressive symptoms when prescribed a drug associated with depression. They should be instructed to report any symptoms of depressed mood or extreme irritability, anxiety, anhedonia, difficulty sleeping, fatigue, feelings of hopelessness or helplessness, change in appetite or weight, or thoughts of death. Patients with a history of depression may be at greater risk for experiencing drug-induced depression. Patients should be encouraged to inform their provider of any history or treatment of any psychiatric disorder.

The FDA requires pharmacists to distribute medication guides to patients receiving medications with specific warnings of suicidality or other severe neuropsychiatric side effects. Medication guides are intended to inform patients about a known serious side effect of a drug. These guides are available at <http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm>.

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