Pharmacological aspects

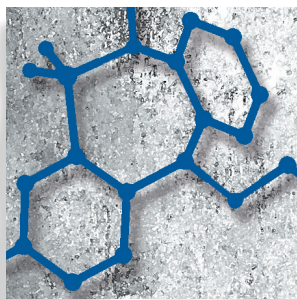# Depressogenic effects of medications: a review

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The literature is filled with reports that link medications with the onset or progression of depression. Because depression is so common in patients with medical illness, assessing whether a medication has in fact caused depression, or whether the relationship is coincidental, can be challenging. In this article, we review the literature on the association between medications and depression. For most agents, there are case reports or small studies linking the medication with the onset of depression, but more rigorous prospective studies are either lacking or found no association between the agent and depression. However, several medications, (eg, barbiturates, vigabatrin, topiramate, flunarizine, corticosteroids, mefloquine, efavirenz, and interferon-α) do appear to cause depression in some patients and should be used with caution in patients at risk for depression.

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Medications can lead to depressive symptoms. These effects can be direct, by altering levels of neurotransmitters in the central nervous system (CNS). Alternatively, they can be indirect, by causing fatigue, diminished appetite, sedation, or other side effects, leading to subsequent frustration, demoralization, or even a full depressive episode. However, it is often difficult to ascertain whether a medication has caused depression in any given patient. Depression is substantially more common in patients with medical illness than it is in the general population. For example, approximately 10% to 20% of patients with acute cardiac disease, diabetes, renal failure, or cancer suffer from current major depressive disorder (MDD), and even more patients have clinically significant, subsyndromal depressive symptoms.[1-4] Therefore, though depression may appear concurrently with one or more medications used to treat medical illness, depression is so common in these patients that this temporal connection may be coincidental. In addition, the vast majority of studies that associate medications with depression have been case reports and case series (not systematic investigations) and have been limited by small and potentially biased samples. Furthermore, these reports typically do not use standardized instruments to evaluate the presence or severity of the apparent depression; they instead rely on general reports of symptoms. Prospective, well-controlled trials examining the links between a medication and depression are relatively rare, and may contradict clinical lore that says that a certain medication causes depression.

In this article, we will carefully examine the links between medications and the onset and progression of

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depression. We have chosen to focus on medications used to treat common conditions (eg, cardiac illness) and on those medications reported to cause depression (eg, isotretinoin [Accutane], corticosteroids). We end with a summary of our findings and provide clinical guidance.

Neurologic medications

Medications for the treatment of seizure disorders

Patients with epilepsy are at significantly increased risk for MDD (6% to 80% prevalence rates) and depressive symptoms when compared with healthy adults or to those with other chronic conditions.[5,6] Thoughts of suicide and suicide attempts have also been associated with the use of anticonvulsants, and they occur with a higher frequency in patients with epilepsy.[6,7] Although a number of factors (including genetics, the location of seizure activity, and psychosocial problems) may contribute to depression, use of anticonvulsant agents may also play a role.[6]

Most anticonvulsants have been linked with the development of depressive symptoms in a small percentage of patients, but three medications (barbiturates, vigabatrin, and topiramate) are thought to be more of a catalyst than others.[5,8] These three medications all work on the γ–aminobutyric acid (GABA) neurotransmitter system and may produce fatigue, sedation, impaired cognition, and depressed mood.[5]

Phenobarbital, one of the oldest barbiturate anticonvulsants, was the first medication to be linked with depressive symptoms.[9,10] In a series of naturalistic studies that followed children with epilepsy over 2 years, Brent and associates[9,10] discovered that even after controlling for stressful life events and family conflict, 40% of phenobarbital-treated patients complained of depression, compared with 4% of carbamazepine-treated patients (P=.02).[10] These rates of depression remained stable over 2 years (38% in phenobarbital-treated patients vs 0% in carbamazepine-treated patients) when phenobarbital was continued, but it frequently resolved upon its discontinuation (P=.05), suggesting a causal role.[9] Although more recent studies of barbiturates have revealed a depression prevalence rate of approximately 10%,[8] depression continues to present a significant problem for these patients, and patients taking barbiturates should be monitored for depression.

Vigabatrin, an anticonvulsant that works by irreversibly inhibiting GABA transaminase and thus increasing CNS GABA levels, has also been associated with depression.[11] A systematic review of double-blind, placebo-controlled trials of vigabatrin found a 12% incidence of depressive symptoms in vigabatrin-treated patients, compared with an incidence of 3.5% in those receiving placebo.[11] Depression associated with vigabatrin therapy can occur at any time during treatment,[12] but it often occurs shortly after treatment initiation or a dose increase[13] and is more likely to occur in those with a history of depression.[12]

Topiramate, an anticonvulsant used for treatment of epilepsy, migraine headaches, smoking cessation, and weight loss, has been linked to the development of depression in approximately 10% of patients.[8,14] The depressive symptoms associated with use of topiramate appear to be dose-dependent, to be more frequent in patients with a personal or family history of depression or other psychiatric illness, and to occur more often after rapid dose escalation.[14,15] In one study, patients who underwent rapid escalation had a 5-fold increased risk of depression development; in patients with a history of depression, this risk increased by 23-fold.[14] Therefore, for patients at increased risk, a slow dose-titration schedule and increased monitoring for depressive symptoms is warranted. Of note, topiramate may be a useful *treatment* for depressive symptoms in the context of MDD or bipolar disorder.[16,17]

Several anticonvulsants (including tiagabine, zonisamide, levetiracetam, and felbamate) have been associated in placebo-controlled trials with depressive symptoms in approximately 4% to 7% of patients.[8] In general, patients at high risk for depression who are prescribed barbiturates, vigabatrin, or topiramate should be monitored for the emergence of depression; a conservative approach to the dosing and titration of medications is also indicated. If a patient develops depressive symptoms while on one of these medications, a switch to a less depressogenic agent may be appropriate.

Medications for the treatment of Parkinson's disease

Like patients with epilepsy, patients with Parkinson's disease (PD) are at increased risk for depression. Most studies estimate that 25% to 45% of patients with PD also suffer from depression[18,19]; this is important as depression is one of the strongest predictors of quality of life in patients with PD.[20] Abnormalities in dopaminergic trans-

mission have consistently been identified as pathophysiological factors that may contribute to the high prevalence of depression in patients with PD[18,19,21]; however, abnormalities in the serotonergic and noradrenergic neurotransmitter systems may also play a role.

The mainstay of therapy for patients with PD is dopamine replacement (typically with levodopa, a dopamine precursor). Levodopa has been suspected of causing depression in a small percentage of patients;[18] one recent study identified a significant increase in depression among patients treated with levodopa for 1 year.[22] Amantadine, an adjunctive agent that appears to potentiate dopamine signaling in the brain, has been associated with depression in a small number of PD patients.[23] However, it also has been shown to have antidepressant properties when used adjunctively with standard depression treatments in patients with PD.[24]

Other dopamine agonists are also used in patients with new-onset PD due to their improved side-effect profiles. Fortunately, none of these medications has been associated with depression; instead, several (eg, pramipexole, ropinirole) have been noted to have antidepressant properties.[25,26] Monoamine oxidase inhibitors (MAOIs) and catechol-o-methyltransferase (COMT) inhibitors (which increase synaptic dopamine levels) also have not been associated with depression. In fact, MAOIs have antidepressant effects and continue to be used for the treatment of MDD. Selegeline, an MAO-B inhibitor, frequently used in patients with PD, has been found to have antidepressant effects in this population.[22]

In summary, depression in patients with PD is common and has a significant impact on quality of life; it should be treated aggressively when it is detected. Fortunately, most medications used for PD have not been associated with depression, and several agents may improve depression. Caution should be taken when using levodopa or amantadine, as these medications appear to increase depressive symptoms most often.

Medications for the treatment of migraine headaches

Depression and migraine headaches frequently co-occur. Patients with migraine headaches have a 2- to 4-fold increased risk for depression,[27] while patients with depression are at a 3-fold increased risk for developing a migraine headache.[28] This bidirectionality suggests that these disorders share a common pathophysiology, most likely involving the serotonergic and GABA-ergic neurotransmitter systems.[29] Depression in these patients not only impacts quality of life, but may also adversely affect the overall prognosis of migraine improvement.[30]

Serotonin agonists (eg, sumatriptan, nalatriptan) are first-line agents for the acute treatment of migraine headaches. To date, these medications have not been associated with the onset of depression and may decrease both depressive symptoms and the frequency and intensity of migraine headaches in patients who suffer from both migraines and MDD.[31] Ergot alkyloids (eg, ergotamine, dihydroergotamine), another acute treatment for migraine headaches, also appear to lack depressogenic effects.

In contrast, flunarizine, a calcium-channel antagonist used for acute and prophylactic treatment of migraine headaches, has been associated with depression. In a randomized, double-blind, prospective study of migraine prophylaxis, 8% of flunarizine-treated patients developed depressive symptoms that led to treatment discontinuation.[32] As a result of this medication's effects on mood and its propensity to cause extrapyramidal symptoms, it now is considered as a second-line treatment for patients with migraines.[32,33]

Prophylactic treatment may be accomplished through the use of anticonvulsants (eg, topiramate, valproic acid), tricyclic antidepressants (TCAs) (eg, amitriptyline), or β-blockers (eg, propranolol), among others. While valproic acid does not appear to increase depression risk, topiramate does.[8] Depression occurs in approximately 10% of topiramate-treated patients; the risk of depression increases significantly in patients with a history of depression and with rapid dose escalation.[8,14,15]

Amitriptyline and other TCAs are effective for treating depression and may be appropriate for treatment of comorbid migraine headaches and depression.[30] Finally, although β-blockers were once thought to cause depressive symptoms,[34-36] recent studies (including a large meta-analysis) have shown that they do not.[37,38]

In sum, there is a strong, bidirectional relationship between depression and migraine headaches. In patients with a history of depression or who are currently depressed, topiramate and flunarizine should be avoided when possible; if treatment with these medications is required, depressive symptoms should be monitored. For these patients, acute treatment with serotonin agonists and prophylactic treatment with TCAs might be considered, as such treatment could alleviate symptoms of both depression and migraine headaches.

Medications for the treatment of multiple sclerosis

Patients with multiple sclerosis (MS) are at significantly increased risk for depression; one study found a 2.3-fold increase in depression risk, even after controlling for age and gender.[39] At present there is no consensus regarding the pathophysiological link between depression and MS; while some researchers suggest increased rates of depression in patients with lesions in specific areas of the brain (eg, right temporal lobe, superior frontal or parietal regions), others have found no such relationship.[40] In patients with MS, depression has been associated with worse quality of life,[41] increased levels of disability,[42] worse adherence to MS treatment,[43,44] and an increased risk of suicide in some studies.[45]

Interferon (IFN)-β-1a and IFN-β-1b are two of the most common disease-modifying agents used to treat MS. Given the risk of depression using IFN-α in patients with HCV infection (see **Anti-infective agents** section), there has been significant concern that IFN-β similarly causes depressive symptoms. Although a few early studies found that IFN-β-1b-treated patients suffered from high rates of depression and suicidal ideation,[43,46] these findings have not been replicated. In a secondary analysis of a double-blind, placebo-controlled study evaluating the efficacy of IFN-β-1a in 365 MS patients, Patten and associates[47] found no significant differences in depression between IFN-β-1a and placebo at 36-month follow-up. Others similarly found no increased risk of depression with IFN-β treatment in patients with MS who were re-evaluated at 65 months; they suggested that pretreatment depression and disability were the biggest predictors of depression at follow-up.[48]

Other agents used in the treatment of MS include 4-aminopyridine, glatiramer, fingolimod, mitoxantrone, and natalizumab. Unfortunately, few data exist regarding the rates of depression in patients taking these medications. Depression, specifically, has been studied for only two of these medications: natalizumab and fingolimod. Two randomized controlled trials (RCTs) of natalizumab found no increased risk of depression.[49,50] A randomized trial of fingolimod similarly found no increase in depression compared with placebo.[51] The incidence of depression in patients treated with mitoxantrone, glatiramer, and 4-aminopyridine has not been specifically studied. However, studies of these medications have found them to be safe and well-tolerated, suggesting that depression may not be a significant side effect of these agents.

Overall, despite the prevalence of depression among patients with MS, medications do not appear to play a role in its development, even in those at risk for depression. Monitoring for depression should be considered for patients on IFN-β; however, the likelihood that it will cause depression is low.

Cardiovascular medications

In this section, we will review the links between depression and a variety of cardiovascular medications; we refer the reader to published reviews of their other neuropsychiatric complications.[52,53]

β-Blockers

A connection between the use of β-adrenergic blockers and depression has long been hypothesized. The lipophilic β-blockers (eg, propranolol and metoprolol) cross the blood-brain barrier much more easily than do nonlipophilic β-blockers (eg, atenolol); as a result, they are thought to be associated with higher rates of neuropsychiatric consequences.

The association between the use of β-blockers and depression remains controversial. Many case reports and several small reviews have linked use of propranolol with depression,[34,35] and a trial by Thiessen and colleagues[36] found that treatment with propranolol was associated with higher rates of antidepressant prescriptions than with other β-blockers (both lipophilic and hydrophilic). In contrast, a RCT of 312 patients who received propranolol found no association between this agent and depression at 1 year.[54] Furthermore, several of the trials listed above did not account for confounding variables (eg, benzodiazepine use and frequency of outpatient visits) that were found to account for the apparent relationship between use of β-blockers and the diagnosis of depression; in one study there was no association between use of β-blockers and depression after accounting for this correction.[55] Finally, a comprehensive review of more than 5800 patients prescribed propranolol found that this agent was rarely associated with depressive symptoms, and that such symptoms typically arose after long-term use.[56]

When trials have been expanded to include use of other β-blockers, the majority of studies and reviews found no association between β-blockers and depression.[37,38] The most extensive analysis of the association between β-

blockers and depression, however, was a meta-analysis of 15 trials of more than 35 000 patients.[37] Ko and colleagues[37] found that β-blockers were not associated with a significant increase in reports of depressive symptoms; furthermore, there were no differences between outcomes following use of lipophilic and nonlipophilic agents. More recent reviews have confirmed this lack of an association.[38]

Finally, pindolol, because of its effects on 5-HT$_{1A}$ autoreceptors, has been actively studied as a potential augmenting agent for patients with depression. A meta-analysis of RCTs of pindolol augmentation of selective serotonin reuptake inhibitors (SSRIs) found that pindolol appears to speed up the response to SSRIs, although it does not appear to improve overall response rates.[57]

Angiotensin-converting enzyme inhibitors

In contrast to β-blockers, angiotensin-converting enzyme (ACE) inhibitors have not been significantly linked with depression. In fact, while several case reports and a small, open trial have found these agents efficacious in the treatment of major depression,[58] larger, randomized trials have not been performed. There are fewer reports of mood effects associated with other ACE inhibitors; in one report, lisinopril was used in the adjunctive treatment of depression.[59] The newer angiotensin-II receptor blockers (ARBs) (eg, losartan, valsartan, and irbesartan) similarly do not appear to have clear associations with depression.

Calcium-channel blockers

Calcium-channel blockers have relatively low rates of adverse neuropsychiatric consequences. Calcium-channel blockers may be associated with fatigue, but they have not been associated with depression.[52,60] Verapamil has been the most-studied calcium-channel blocker for mania and bipolar disorder and it has had mixed, but generally positive, results; this agent may be a viable option for patients with bipolar disorder who are pregnant or who fail first-line therapies.

Calcium-channel blockers have been studied in the treatment of depressive symptoms, with only modest results. Verapamil was less effective than amitriptyline (a TCA) in a double-blind trial for depression,[61] and ineffective for depression among patients refractory to

TCAs.[62] Furthermore, because calcium-channel blockers may be effective in the treatment of cerebrovascular disease, nimodipine has been used to augment antidepressant treatment in patients suffering from vascular depression (ie, new-onset depression in older adults associated with vascular lesions) in double-blind, placebo-controlled studies.[63] Both studies found that the addition of nimodipine was superior to placebo in reducing depressive symptoms and in lowering rates of recurrence.

Diuretics

Diuretics are generally associated with low rates of neuropsychiatric adverse events. One series of eight patients reported a link between use of thiazide diuretics and depression,[64] although further evidence for this association is lacking. Other diuretics have relatively few neuropsychiatric effects. Loop diuretics (such as furosemide and ethacrynic acid) have not been associated with mood syndromes. Epstein and Grant[65] found that nearly half of carbonic anhydrase-inhibitor-treated patients had a mild syndrome of fatigue, malaise, anorexia, and depression, and that such symptoms were associated with acidosis.

Centrally acting antihypertensive agents

Clonidine, a central α-adrenergic agonist, is associated with a number of neuropsychiatric effects; fatigue and sedation are the most common effects, with sedation occurring in one third or more of patients.[53] Rarely, mood disturbance has been described with clonidine; pooled information suggests that depression occurs in approximately 1% to 2% of patients. There are no case reports of clonidine-induced depression or mania, though there has been one report of hypomania upon withdrawal of clonidine.[66]

Methyldopa, another centrally acting antihypertensive medication, is infrequently used in clinical practice (except in those with pregnancy-induced hypertension). It may reduce blood pressure via central α-$_2$ agonism, and may also act as a false (norepinephrine) neurotransmitter.[53] As with many cardiovascular agents, common side effects are sedation and fatigue; sedation occurs in approximately one third of methyldopa-treated patients, with high rates of associated fatigue.[67] However, perhaps the best-known neuropsychiatric consequence of methyldopa use is

depression. Depressive symptoms may occur more frequently with methyldopa than with most other antihypertensive agents, and it is thought that this effect may be related to reduced norepinephrine levels. An early study of methyldopa found increased rates of depression, especially in those with a history of depression,[68] and a study of elderly patients found methyldopa to be more strongly associated with depressive symptoms than were β-blockers[69]; overall, it appears that reported depressive reactions to methyldopa often occur in those with prior depressive episodes.[70] In contrast, a review of the literature by Long and Kathol[71] found no clear evidence that methyldopa (in contrast to reserpine) was associated with depressive symptoms. Similarly, a review of 80 patients found no significant association between methyldopa and depression.[72]

Reserpine

Reserpine, an older antihypertensive medication that is now rarely used, can have a variety of neuropsychiatric effects. This agent acts by inhibiting the sequestration of monoamine neurotransmitters into storage granules, resulting in the metabolism of these neurotransmitters by monoamine oxidase (MAO). This depletion of catecholamine neurotransmitters results in its antihypertensive effects and likely contributes to its association with depression.[53]

Reserpine has long been associated with depressive symptoms with a number of reports in the 1950s that linked reserpine use with depression,[73] and a later review citing an incidence of up to 15%.[74] However, other (generally more recent) reports call this association into question. First, the depressive symptoms associated with use of reserpine appear to include sedation, malaise, and fatigue.[53,75] Patients with these symptoms alone may not meet formal criteria for major depression but instead exhibit subsyndromal depression.[53,75] Those who do meet full criteria tend to receive higher doses and to have a history of depression. Furthermore, two relatively large studies (one with over 4000 patients examining the onset of depressive symptoms among patients taking diuretics, β-blockers, and reserpine,[76] and the other of elderly individuals with hypertension who used low doses of reserpine),[77] found very low rates of depression with reserpine use. In summary, reserpine is associated with fatigue and sedation in a substantial subset of patients, and may be associated with depressive symptoms, although this latter association is neither as strong nor as clear as was once thought.

α-Adrenergic agents

The α_1-adrenergic antagonists (eg, prazosin, doxazosin, and alfuzosin) are used as antihypertensive agents and to treat symptoms of benign prostatic hypertrophy. In general, there are few adverse neuropsychiatric consequences associated with these medications. Depression has not been consistently associated with this class of agents, although there have been rare reports associated with prazosin use. Prazosin has been increasingly studied in the treatment of post-traumatic stress disorder (PTSD).

Vasodilators

Hydralazine, a systemic vasodilator whose use is usually reserved for patients with severe hypertension, on occasion has been linked with neuropsychiatric side effects. Rarely, hydralazine has been associated with the onset of depression[52]; overall it is not linked to mood disturbance. Nitrates (eg, nitroglycerin, isosorbide dinitrate, and nitroprusside), most commonly used to treat angina, have minimal neuropsychiatric side effects. However, a single case report has described hallucinations and suicidal ideation in a patient taking isosorbide dinitrate.[78]

Antiplatelet and anticoagulant agents

Aspirin (salicylic acid) has few neuropsychiatric consequences. The anti-inflammatory effects of aspirin have been postulated to have potential benefit in depression, given recent suggestions that inflammation may contribute to the pathophysiology of this disease. The antiplatelet agent clopidogrel has not been associated with significant neuropsychiatric consequences. Similarly, the anticoagulant medications, heparin and warfarin, are not commonly associated with neuropsychiatric effects, nor are enoxaparin or the glycoprotein IIb/IIIa inhibitors.

Selected antiarrhythmic medications

Amiodarone

Thyroid abnormalities—including hypothyroidism and hyperthyroidism—occur in approximately 15% of patients taking amiodarone due to its high iodine content and its direct toxic effects on the thyroid.[79] Through

this indirect mechanism, neuropsychiatric effects of amiodarone may occur, as hypothyroidism may cause fatigue and depressive symptoms,[80] and hyperthyroidism can (more rarely) be associated with depressive symptoms.[81] Amiodarone has also, on occasion, been directly linked with depressive symptoms.[82,83]

Digoxin

Digoxin has been associated with a wide variety of neuropsychiatric side effects, at both toxic and therapeutic levels (see Keller and Fishman's excellent review).[53] Although such effects include depression (the prescribing information for digoxin reports "mental disturbance" in 5% of patients taking digoxin as opposed to 1% with placebo), delirium and psychosis are far more common with this agent.[84] Depressive symptoms have been associated with digoxin in small trials and case reports, and digoxin toxicity can masquerade as depression.[85] Depression linked with use of digoxin presents with prominent fatigue, low appetite, and impaired sleep. Despite these reports, however, larger prospective trials have not supported a strong link between use of digoxin and depression.[86,87]

Lipid-lowering agents

The HMG-CoA reductase inhibitors ("statins"), the most commonly used lipid-lowering agents, have been associated with few neuropsychiatric effects.[88] Lovastatin and pravastatin are more lipophilic than are other agents (eg, atorvastatin and pravastatin); however, clinical experience has not found great differences between these agents.

Low cholesterol levels have been correlated with depression and suicide in several longitudinal studies, with one study noting a 4- to 7-fold increase in risk of severe depressive symptoms in men with chronically low cholesterol levels.[89] Despite these findings, lowering serum cholesterol with statins has not been associated with increased rates of depression, noncardiac deaths, or suicide in several large prospective studies.[90,91] Overall, there have been only a handful of reports of depressive symptoms associated with statin use,[92] and prospective studies and reviews of statins' effects on mood have found that these agents do not consistently cause depression.[88,93] The lipid-lowering agents gemfibrozil and niacin have not been systematically associated with depression,

although idiosyncratic depressive reactions are possible; bile acid sequestrants (eg, cholestyramine) similarly have low rates of associated neuropsychiatric effects, including depression.[94]

Summary

In summary, the vast majority of the association between depression and cardiovascular medications are documented by case reports and open trials that are unable to definitively answer questions about causality. Many cardiovascular agents cause fatigue and sedation (which may mimic depression) at rates greater than with placebo, and case reports of medication-induced mood syndromes exist for many cardiovascular drugs. Depression has been associated with β-blockers, methyldopa, and reserpine, but more recent syntheses of the data have suggested that these associations are much weaker than originally believed, especially when more comprehensive prospective trials have been performed. Though low cholesterol has been associated with depression and suicide, lipid-lowering agents have not been associated with these adverse effects.

Anti-infective agents

In an infected, medically ill, withdrawn patient, differentiating among illness effects, psychological responses to illness (eg, demoralization), and medication side effects (including neuropsychiatric manifestations) can be difficult. Acutely ill, infected individuals often complain about malaise, dysphoria, fatigue, and insomnia; together these symptoms can be confused with a clinical syndrome of depression and be attributed to the most recent medication added to the regimen (which will often be an anti-infective agent). In such a scenario, cytokine-driven sickness behavior can account for much of the observed psychopathology and subjective misery[95,96] and will often offer a better explanation than will medication-induced depression. In addition, in a withdrawn patient, a hypoactive delirium secondary to an infection might be mistaken for "depression."[97]

Antibiotic medications

Most antibiotics used to treat infections are well tolerated and are unlikely to cause MDD. Nonetheless, isolated case reports (eg, "fluoroquinolone-induced depres-

sion") describe the development of depressive symptoms.[98] Interestingly, some antibiotics have even played a role in the development of effective, modern antidepressants (eg, isoniazid),[99] and some antibiotics (including the β-lactam, ceftriaxone) are currently being investigated as antidepressants due to their effect on glutamate transmission.[100] Numerous case reports link anti-infective agents to depression (including antituberculous agents [eg, cycloserine, ethionamide], metronidazole, or quinolones).[101] Antituberculosis agents (eg, isoniazid, cycloserine, and fluoroquinolones) have been associated (rarely) with seizures and psychosis; these manifestations, if left unrecognized, could be mistaken for depression.[102]

Antiretroviral medications

Effective treatment for Human Immunodeficiency Virus (HIV) infection/Acquired Immunodeficiency Syndrome (AIDS) involves the use of combination antiretroviral therapies (cART). One commonly used first-line cART regimen includes the non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz. Among the antiretroviral agents, efavirenz has been frequently associated with neuropsychiatric side effects (eg, vivid dreams, anxiety, depressive symptoms).[103] Such side effects seem to be transient in most patients[104] and dose-related.[105] Moreover, a polymorphism in the CYP2D6 gene has been associated with efavirenz plasma concentrations.[106] While genotype-based dose reduction was reported as a successful strategy in reducing efavirenz-associated CNS symptoms,[107] the role of pharmacogenetics and therapeutic drug monitoring (TDM) for optimal efavirenz dosing needs further refinement.

Some medications used in the treatment of HIV-infection/AIDS might mimic depression. The first antiretroviral agent to treat HIV infection, zidovudine (AZT), for example, causes fatigue associated with significant anemia.[108] AZT has also been linked with a variety of CNS effects (including insomnia, restlessness, and irritability) that can be mistaken for manifestations of agitated depression, if the reasonably well established AZT-induced mania is missed.[109]

Interferon-α

IFN-α, in combination with ribavirin, is an effective treatment for chronic hepatitis C virus (HCV) infection.

IFN-α is the prototype for a chemically-induced bona fide depressive syndrome; it induces significant depressive symptoms in up to 58% of patients,[110] disrupts sleep continuity, and increases evening cortisol.[111] The pathophysiology of interferon-induced depression is likely related to IFN's induction of a key enzyme of tryptophan catabolism, indoleamine 2,3-dioxygenase (IDO).[112] IDO activation has downstream consequences, including an increase in brain kynurenine, which correlates with depressive symptoms.[112]

Depression that emerges during HCV treatment with IFN-α is a dreaded complication that can lead to early treatment discontinuation.[113] In one prospective study of 162 patients (who were regularly assessed with a self-rating depression scale [the Zung Self-Rating Depression Scale] for the duration of a 24-week treatment trial), depression at baseline was the best predictor of the eventual development of moderate to severe depression.[114] Randomized trials of serotonergic antidepressants for prophylactic treatment of depression have shown mixed results, with most studies failing to show a clear benefit.[115,116] However, it is reassuring to know that patients who develop depression during IFN-based treatment for HCV respond to initiation of an antidepressant agent.[117]

Antimalarial medications

Among commonly employed prophylactic malaria regimens, use of mefloquine has most often been considered as (in prospective, randomized trials) a stimulus for depression. Van Riemsdijk and colleagues[118] found higher depression scores and fatigue in patients randomized to prophylactic mefloquine in comparison to atovaquone plus chloroguanide. A four-arm trial comparing mefloquine, atovaquone-proguanil, chloroquine-proguanil, and doxycycline revealed the highest rate of neuropsychological manifestations in the mefloquine arm, particularly among women.[119] A more detailed analysis found similar mood profiles for all four treatment groups (with the exception of women using mefloquine, who showed more fatigue and confusion).[120] This gender-specific vulnerability to side effects is consistent with a genetic study that examined polymorphisms in the *MDR1/ABCB1* gene (encoding for the efflux pump P-glycoprotein) and which found an association between a particular haplotype and neuropsychiatric side effects of mefloquine that were limited to females.[121] By con-

trast, one large, observational study was unable to confirm an increased risk of depressive symptoms associated with mefloquine when compared with prophylactic use of other antimalarials.[122]

Antifungal medications

Amphotericin B (used for serious, systemic fungal infections like cryptococcal meningitis in immunocompromised patients) has been associated with acute CNS toxicity, including "delirium and depression."[123]

Summary

In a comprehensive literature review, Patten and Barbui[124] identified only IFN-α and mefloquine as the anti-infective drugs that had good evidence for being a causative agent for depressive symptoms. To this list, we would add the antiretroviral, efavirenz. Patten and Barbui[124] further concluded that many reports of so-called medication-induced depressions merely describe isolated, nonspecific neuropsychiatric symptoms (eg, insomnia, malaise) but not a full depressive syndrome. Anti-infective agents can appear "depressogenic" if they are given to a patient with delirium or if they contribute to the development of delirium. Moreover, both depression and anxiety are commonly seen as delirium resolves; such post-delirium mood states should not be attributed to the medications responsible for the delirium itself.[125]

Oncologic medications

The association between cancer and psychiatric disorders has been repeatedly documented; approximately 10% to 25% of cancer patients develop MDD or significant depressive symptoms.[3] As with other medical conditions, the diagnosis of depression in patients with cancer is often challenging, since several somatic symptoms of depression overlap with those of cancer and the side effects of its treatment.

Many researchers have investigated the incidence of depression in patients undergoing chemotherapy regimens. Except for a few agents, evidence of chemotherapy-induced depression is scarce. However, the conclusions are controversial. Further complicating the assessment is the use of multiple agents in treatment protocols (often involving corticosteroids) and a lack of standardized depression measures across studies.

Chemotherapy agents

Alkylating agents

The evidence for the depressogenic effects of alkylating agents (eg, procarbazine, carmustine, busulfan) is sparse. Nevertheless, depression is listed as an adverse reaction to procarbazine in several textbooks and in its product insert.[126] However, only one report describes the development of "depression and lassitude."[127] Furthermore, no prospective reports focus directly on the incidence of MDD with this agent; interestingly, this agent is a weak MAOI that has been associated with mania and serotonin syndrome.

Phase II trials of carmustine have reported that depression occurs in up to 16% of carmustine-treated patients (compared with 10% of those receiving placebo); however, this information is derived from questionnaires about toxicity and not from standardized psychiatric evaluations.[128] Likewise, depression was reported in 23% of patients receiving busulfan in clinical trials, when busulfan was employed as part of the treatment for stem cell transplant recipients.[129]

Vinca alkaloids

In vitro, vinca alkaloids almost completely inhibit the release of dopamine-β-hyroxylase, thereby interfering with the conversion of dopamine to norepinephrine[130]; this process has been linked with the development of irritability and depression in patients receiving vincristine[131] and vinblastine.[132]

Antimetabolites

Antimetabolite drugs interact with specific enzymes by inhibiting the enzyme or causing the synthesis of aberrant molecules that cannot function normally. Pemetrexed, an antifolate antimetabolite, has been reported to cause mood disturbances (including depression). One large multicenter phase III trial found depressive symptoms in 11% of those receiving pemetrexed.[133] Another multicenter study examined a regimen of pemetrexed and cisplatin and found a 14% rate of occurrence.[134]

Depression has been listed among the adverse reactions to fludarabine, another antimetabolite; however, this has not been reported often during controlled trials that

have looked at its safety and efficacy. Furthermore, one study examining the safety of oral fludarabine showed a statistically significant improvement in the mean scores of emotions among patients who received this agent.[135]

Medications that interfere with DNA and RNA synthesis

Doxorubicin and daunorubicin are anthracyclic antibiotics that act by binding to DNA and disordering synthesis. Based on animal models, this class of medications is potentially neurotoxic; however, at therapeutic doses in humans these agents do not cross the blood-brain barrier. Depression is not commonly associated with these agents; nevertheless, one prospective, randomized phase III trial (comparing doxorubicin and daunorubicin for the treatment of Kaposi's sarcoma), reported the incidences of depression as 6% and 10%, respectively.[136] L-Asparaginase (a naturally occurring enzyme that inhibits protein, DNA, and RNA synthesis in tumor cells by decreasing circulating levels of asparagine) has been associated with assorted psychiatric symptoms (including irritability, depression, and hallucinations). Haskell and colleagues[137] reported that up to 31% of patients taking this medication developed CNS abnormalities (most commonly moderate to severe depression associated with personality disturbances). Ohnuma[138] reported that 25% of patients developed mild depression and drowsiness within 1 month of therapy; higher doses were related with more severe symptoms, and discontinuation of it led to the resolution of symptoms.[139]

Mitotic inhibitors

Taxane drugs (ie, paclitaxel and docetaxel) are mitotic inhibitors that interfere with the normal breakdown of microtubules during cell division. Several studies have found an association between these medications and depressive symptoms. One case report of a woman receiving paclitaxel described the onset of severe depression and suicidal thoughts that remitted following the discontinuation of the drug.[140] In a prospective RCT, Fountzilas and associates[141] reported worse emotional function in those receiving paclitaxel as part of a multidrug regimen as compared with those receiving the same regimen without paclitaxel. Finally, in a naturalistic, longitudinal study, Thornton and coworkers[142] documented slower psychological recovery and higher rates of depressive symptoms in patients receiving paclitaxel and docetaxel.

Biological agents

Interleukins

Interleukin-2 (IL-2) has been used in the treatment of metastatic renal cancer, melanoma, and other malignancies. Early observations reported the development of clinically significant neuropsychiatric changes during treatment with IL-2; behavioral and cognitive changes (including elevated depression scores) appeared to be dose-related. Walker and coworkers[143] found higher scores in the Hospital Anxiety and Depression Scale in patients receiving IL-2 therapy used for advanced colorectal cancer (compared with those on standard chemotherapy). Finally, Capuron and colleagues[144] found elevated depression scores in patients receiving IL-2, potentially reflecting authentic changes in mood states rather than somatic symptoms alone. In a later study, the same authors showed that mood symptoms correlated with increased serum cytokine levels during treatment.[145]

Corticosteroids

Corticosteroids are used to treat the symptoms of a number of neurologic (eg, MS), rheumatologic (eg, rheumatoid arthritis), gastrointestinal (eg, Crohn's disease, ulcerative colitis), and respiratory (eg, chronic obstructive pulmonary disease, asthma) diseases characterized by excessive inflammation. They also are commonly indicated in oncologic patients, both to reduce inflammation around tumors as well as to reduce the side effects induced by chemotherapy agents. These agents have been associated with a broad range of neuropsychiatric symptoms, varying from subtle anxiety/depression to full-blown affective and psychotic disorders. Early studies suggested these side effects were dose-dependent.[146] Depressive disorders are commonly associated with long-term corticosteroid therapy. One study found that chronic corticosteroid-treated patients had significantly greater depressive symptom severity as well as global psychiatric symptom severity, and a 60% lifetime risk for mood and anxiety disorders.[147] Breitbart and associates[148] examined the impact of steroids in cancer patients, and found an increased incidence of depressive disorders in patients receiving high-dose dexamethasone for the treatment of spinal cord compression. The authors noted psychological stress increased as the

dosage was tapered, and it was difficult to determine whether symptoms resulted from dose-reduction of cumulative steroid exposure. Corticosteroids are thought to induce mood symptoms by elevating plasma cortisol concentrations; interestingly, hypothalamic-pituitary-adrenal axis dysfunction has been strongly associated with the development of depression in cancer patients.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors have potent activity against a variety of tyrosine kinases, each with specific molecular targets and mechanisms of action. The prescribing information for several of these agents lists depression as an adverse effect. Early trials of imanitib found depressed mood to occur in 7% to 15% patients, with more severe depressive symptoms (with significant dysfunction or suicidal ideation) occurring in less than 1% of patients.[149] However, a meta-analysis of clinical trials using imatinib for the treatment of chronic myeloid leukemia did not report depression among the commonly encountered side effects.[150] Quek and associates[151] reported seven previously healthy patients who developed depression within 6 months of starting treatment with imatinib and dasatinib; in all cases, symptoms improved after dose reduction and discontinuation of the drug. In two of these cases, symptoms reappeared after a drug rechallenge. Similarly, depressed mood is listed as an adverse reaction in the prescribing information for cetuximab, dasatinib, sorafenib, and sunitinib; meta-analysis of clinical trials and literature reviews of these agents do not report any data on the statistically significant occurrence of depressive symptoms. Finally, using a standardized tool, Pirl and associates[152] failed to find a statistically significant association between depressive symptoms and concomitant use of gefitinib or erlotinib.

Hormonal agents

Estrogen and testosterone deficiencies have been linked to MDD. Presumed mechanisms include alteration of the concentration and availability of neurotransmitters amines, including serotonin. Treatment of hormone-sensitive tumors involves use of medications aimed at reducing availability of sex hormones. Studies evaluating the association between depression and treatment with tamoxifen have yielded diverse results. In some trials, a subset of patients have discontinued tamoxifen

therapy because of depressive symptoms, whereas in other studies, conducted primarily in the breast cancer prevention setting, no increased risk of depression was observed during treatment.[153]

Similarly, studies on aromatase inhibitors have yielded mixed results. A large clinical trial involving 9366 postmenopausal women with localized breast cancer compared anastrozole and tamoxifen; they reported depressive symptoms occurring in 19.3% of patients treated with anastrozole.[154] However, subsequent studies have not replicated these findings. Finally, gonadotropin releasing hormone (GnRH) agonists (ie, leuprolide and goserelin), have been associated with depression in non-cancer populations. Clinical trials in prostate cancer patients have showed diverse results, and well-controlled prospective studies have suggested that depression occurs, although fatigue is more prevalent and may be mistaken for depression.[155]

Miscellaneous medications

Isotretinoin

Patients with acne are at an increased risk for depression, with prevalence rates of up to 30% reported in patients who suffer from moderate to severe acne.[156] One of the most effective treatments for nodulocystic acne, isotretinoin (a synthetic oral retinoid medication), became a source of significant concern due to its potential link with the development of depressive symptoms. Evidence for concerns about depressive symptoms and suicidal ideation came primarily from case reports and case series.[157] More recently, however, these claims have been challenged by the results of both retrospective and prospective trials. In a systematic review of nine studies evaluating the psychiatric effects of isotretinoin, Marqueling and associates[158] found no association between the use of isotretinoin and depression. Approximately 1% to 11% of isotretinoin-treated patients developed depressive symptoms (a rate similar to that found in patients receiving oral antibiotics).[158] Subsequently, prospective studies have provided further evidence for lack of an association between isotretinoin and depression[159,160]; only one study has found an increased risk for depression.[161] However, existing prospective studies may not be large enough to detect subtle increases in depression rates; therefore, while there does not appear to be a significant increase in

depression risk associated with the use of isotretinoin, cases of depression may still be attributed to isotretinoin treatment.

Medications for the treatment of infertility

Infertility, occurring in approximately 10% to 14% of women, represents a significant life stressor for affected women.[162] Although the results are mixed, some studies have shown that depression in infertile women is twice as high as it is in fertile women.[163] Abnormalities in the hypothalamic-pituitary-gonadal axis, infertility-associated stress (with subsequent elevation in stress hormone levels), and use of medications to treat infertility may all contribute to depressive symptoms.[162] In a recent review, Wilkins and associates[162] noted three classes of fertility medications associated with depression: oral contraceptives containing progesterone, gonadotrophin-releasing hormone agonists (eg, leuprolide), and clomiphene citrate.[162]

Oral contraceptive pills (OCPs) and depot contraceptives have long been associated with depression.[164] Several factors (eg, a personal history of psychiatric illness, a family history of OCP-related mood complaints, and a propensity for hormone-related mood symptoms [eg, premenstrual or pregnancy-related emotional changes]) have been considered to increase the risk of depression.[165] However, more recent data from RCTs have failed to confirm the association seen in these earlier studies. In a retrospective analysis of 290 patients with a history of depression, those who were on combination OCPs or progestin-only contraceptives had less severe depression, fewer comorbid anxiety disorders, and better physical function than patients not taking contraceptives.[166] These findings were confirmed prospectively by O'Connell and associates,[167] who performed a double-blind, randomized, placebo-controlled trial of combination OCPs in 76 adolescents (finding fewer depressive symptoms in patients on OCPs). Therefore, the results regarding the impact of contraceptive medications on a propensity to depression are inconclusive.

GnRH agonists (such as leuprolide and goserelin) can have a number of psychiatric effects. Although these medications have been used successfully for the treatment of premenstrual syndrome (including feelings of sadness) in some patients,[168] in other patients these medications have been associated with depression.[169] In the original studies by the manufacturer, 22% of leuprolide-treated patients and 54% of goserelin-treated patients suffered from significant depressive symptoms.[170,171] These findings (for both medications) have been replicated in subsequent case series.[172,173] Furthermore, a retrospective study found that approximately 80% of patients treated with leuprolide suffered from significant depressive symptoms (eg, Hamilton Rating Scale for Depression-21 score ≥20).[174] However, a lack of prospective studies makes it difficult to identify the risk associated with these medications. Interestingly, prophylactic treatment with SSRIs appears to prevent the development of depressive symptoms in these patients.[169,174]

Clomiphene citrate, a selective estrogen receptor modulator used to induce ovulation, has been associated with mood lability and depressed mood in two cross-sectional studies.[175,176] In the larger of these studies, 67 of 162 (41%) of clomiphene-treated women experienced depressed mood and 75 of 162 (45%) experienced mood swings during treatment.[176] Unfortunately, there are no prospective studies that evaluate the association between clomiphene and psychiatric symptoms; nevertheless, given the evidence from cross-sectional studies, care should be taken when prescribing this medication to infertile women.

In sum, there is mixed evidence regarding the depressogenic effects of medications for the treatment of infertility. Although progesterone-containing contraceptives caused the most concern through case reports and retrospective studies, systematic prospective studies have revealed that these medications are rarely linked to depressive symptoms. Preliminary cross-sectional and retrospective studies also suggest a possible link between depression and the use of GnRH agonists and clomiphene citrate; however, prospective studies will be required to confirm these associations.

Varenicline

Varenicline, a nicotinic receptor partial agonist, is used clinically to facilitate smoking cessation. Since its introduction, it has been scrutinized as several case reports and retrospective studies have noted worsening mood and suicidal ideation during its use[177,178]; these findings have led to a Food and Drug Administration warning about varenicline.[179] However, large observational cohort studies have failed to confirm an increase in depression or suicidal risk[180,181]; further, an open-label study found a significant

decrease in depressive symptoms during treatment with varenicline.[182] The finding that smoking cessation itself can precipitate depressive symptoms in patients with nicotine dependence may partly explain the early case reports linking varenicline and depression.[183] Therefore, while idiosyncratic depressive reactions are possible during treatment with varenicline, there is no clear evidence that this medication is depressogenic. Further studies should be performed to further clarify these findings.

Conclusions

The medical literature is replete with reports of depression caused by a certain pharmacologic agent. As noted, these reports are often compromised by small or biased samples, lack of standardized depression assessments, and by the high prevalence of depression in the medically ill. Often, when prospective studies are performed, these agents do not in fact appear to cause depression in most patients, and their use should not be avoided in patients at risk for depression, especially if they are important for the treatment of the underlying medical condition. Unfortunately, few prospective studies—especially challenge-dechallenge-rechallenge trials—have been performed to evaluate the psychiatric effects of medications purported to cause depression. The lack of confirmation by prospective studies highlights the importance of the systematic evaluation of psychiatric

side effects of medications, as basing clinical practice on case reports often can lead to withholding beneficial treatments for fear of rare side effects.

However, some agents appear to cause depression in a minority of patients. These agents include barbiturates, vigabatrin, topiramate, flunarizine, corticosteroids, mefloquine, efavirenz, and IFN-α. These agents should be used more cautiously in patients with current or prior depression, or those who are otherwise at high-risk for depression. Depression is rarely an absolute contraindication to the use of a medication, but several factors should be weighed by clinicians to make the best prescribing decision for a given patient. These factors include the extent of potential benefit of the medication on the medical condition, the existence of nondepressogenic alternative medications to treat the condition, the patient's history of depression (and severity of prior depressive episodes), and the ability to monitor the patient for depression.

Finally, one final clinical caveat: though a certain medication may not cause a depressive syndrome in the general population, idiosyncratic reactions can occur as the result of genetic vulnerabilities and environmental stressors (eg, concurrent medications). Therefore, if a patient develops depressive symptoms after the initiation of a given agent (especially after an 'on-off-on' trial suggesting consistent onset of depression with the medication), another agent should be strongly considered. ❏

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Efectos depresógenos de los medicamentos: una revisión

La literatura está llena de reportes que relacionan los medicamentos con el inicio o la progresión de la depresión. Dado que la depresión es tan frecuente en pacientes con enfermedad médica, puede ser desafiante el evaluar si un medicamento de hecho ha causado la depresión o si la relación es sólo una coincidencia. En este artículo se revisa la literatura relacionada con la asociación entre medicamentos y depresión. Para la mayoría de los fármacos hay reportes de casos o pequeños estudios que vinculan la medicación con el inicio de la depresión, pero estudios prospectivos más rigurosos no existen o no encuentran asociación entre el fármaco y la depresión. Sin embargo, varios medicamentos (por ejemplo, barbitúricos, vigabatrina, topiramato, flunarizina, corticoides, mefloquina, efavirenz e interferon-alfa) parecen causar depresión en algunos pacientes y deben utilizarse con cautela en pacientes con riesgo de depresión.

Une analyse des effets dépressogènes des médicaments

La littérature regorge de rapports qui relient les médicaments à la survenue ou à la progression d'une dépression. La dépression étant très courante chez les personnes malades, l'évaluation de l'implication du médicament dans l'installation de la dépression, ou de la coïncidence de la relation observée, peut s'avérer difficile. Dans cet article, nous effectuons une revue des liens entre médicaments et dépression. Pour la plupart des produits, des rapports de cas ou de petites études associent le médicament à la survenue de la dépression, mais il manque des études prospectives plus rigoureuses ou celles qui existent n'ont pas trouvé de lien entre le produit et la dépression. Cependant, plusieurs médicaments (barbituriques, vigabatrine, topiramate, flunarazine, corticoïdes, méfloquine, éfavirenz et interféron-α) semblent provoquer une dépression chez certains patients et doivent être utilisés avec précaution chez les patients ayant un risque de dépression.

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