Medications With Depression as an Adverse Effect

To the Editor In a cross-sectional survey study, Dr Qato and colleagues1 found that the use of prescription medications with depression as a potential adverse effect was common. However, the authors did not take into account that most of the drugs described are used to treat conditions already linked to an increased risk of depressive symptoms. Although they investigated the relationship between hypertension and depression, they did not account for the association of depressive symptoms with pain (and subsequent use of pain killers), gastroesophageal reflux disorder (and subsequent use of gastrointestinal agents), or atopic disorders, such as asthma or allergic rhinitis (and the use of montelukast and antihistamines). Interestingly, these conditions are related to persistent low-grade inflammation,2 an important factor associated with depression, which could not be accounted for in the study.

The increase in prescription of such drugs follows the increased prevalence and survival of people with chronic conditions in the United States.3 In Table 1 in the article, the patients taking drugs associated with depression included more women, older people, widowed or divorced people, and people with higher levels of unemployment and obesity, factors also associated with an increased risk of depression in nonmedicated populations. This group also had more comorbidities, which may have additive inflammatory and psychological effects. People with more than 1 medical comorbidity tend to have more depressive symptoms, increasing with the number of disorders, without the etiology being related to adverse drug reactions.4

The study did not investigate the converse—drugs that can be associated with a reduction in risk of depressive symptoms. Anti-inflammatory drugs or drugs for other conditions that exhibit anti-inflammatory properties, such as statins, acetylsalicylic acid, some hypoglycemic agents, drugs that act in the renin-angiotensin-aldosterone system, and immunomodulators, may have beneficial effects on mood, at least in subgroups of people.5

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Additional Contributions: We thank Denna Wheeler, PhD, from the Oklahoma State University Center for Health Sciences, who was not financially compensated, for assistance with statistical analysis.


COMMENT & RESPONSE

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To the Editor Dr Qato and colleagues1 studied common prescription drugs associated with depression as an adverse effect. The authors controlled for the number of self-reported chronic conditions and performed sensitivity analysis of patients with hypertension. However, one factor that may play a role in the results that the authors did not discuss is the severity of illness of the patients.

More severe forms of chronic illnesses, such as hypertension, can be associated with higher levels of depressive symptoms.2 Could it be that more severe forms of disease are associated with the use of drugs that have depression listed as an adverse effect? Clinicians may be less likely to prescribe certain drugs unless a condition is severe and is uncontrolled with other, more benign medications. For instance, in primary care in the United Kingdom, most patients with hypertension are not prescribed β-blockers unless their hypertension is uncontrolled with other agents. While the sensitivity analysis of patients with only hypertension showed a statistically significant difference between those taking...
different types of drugs, it cannot take into account the severity of the condition. Could chronic illness severity be a confounder and play a role in causing depression, the choice of drugs prescribed, and any resultant association?

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported owning stock in GlaxoSmithKline.


In Reply Drs Agustini and Berk raise 3 primary concerns regarding our analysis demonstrating an association between the use of prescription medications with depression as a potential adverse effect and concurrent depression.

Their first concern is that we did not account for the association between depression and other health conditions besides hypertension—particularly conditions related to inflammation, such as pain and asthma, which are often treated with medications, such as pain killers and antihistamines that are associated with depressive symptoms. However, not all commonly used medications to treat these conditions, including hypertension, are associated with an increased risk of depressive symptoms. Specifically, many of the most frequently used nonsteroidal anti-inflammatory drugs (eg, ibuprofen), antihistamines (eg, cetirizine), and proton pump inhibitors (eg, omeprazole and esomeprazole) were on our list of prescription medications with depression as a potential adverse effect, although some nonsteroidal anti-inflammatory drugs (eg, naproxen), antihistamines (eg, loratadine), and proton pump inhibitors (eg, pantoprazole) were not.

Their second concern focuses on the importance of accounting for sociodemographic characteristics, including age, employment status, marital status, and comorbidity profiles of adults. In all our adjusted analyses, we accounted for these sociodemographic characteristics and comorbidities, measured as number of chronic conditions. In these adjusted analyses, we only observed a dose-response association between the number of medications used and concurrent depression for medications that have (vs do not have) depression as a potential adverse effect.

Their third concern is that we failed to incorporate information in our analyses on prescription medications that may reduce the risk of depression, particularly those that exhibit anti-inflammatory properties. We recognize the importance of the evolving literature on the role of inflammation and anti-inflammatory drugs in depression. Although inflammation does not appear to be necessary or sufficient for the development of depressive symptoms for everyone, there may a subset of vulnerable individuals in whom inflammation plays an important role.

Dr Burch asserts that more severe forms of chronic illness, including hypertension, may be associated with a higher risk of depression and that we did not incorporate severity in our analyses. While we agree that disease severity may be an important confounder, evidence demonstrating an association between disease severity and depression is lacking, including for hypertension.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Qato reported receiving a grant from Janssen Scientific Affairs LLC to Columbia University Medical Center.


Stress-Related Disorders and Autoimmune Disease

To the Editor Dr Song and colleagues reported that stress-related disorders were associated with increased risk of subsequent autoimmune disease. Stress is an adverse event that is associated with various mental disorders and physical diseases, possibly through hypothalamic-pituitary-adrenal axis dysregulation, epigenetic modification, or the inflammatory response. The study presented several problems that require further discussion.

First, in individuals with a history of other psychiatric disorders, Song and colleagues discovered that the risk of autoimmune disease was increased among patients with stress-related disorders, compared with matched individuals without stress-related disorders, but the risk of autoimmune disease was not increased compared with full siblings (eg, for all stress-related disorders, hazard ratio, 1.05; 95% CI, 0.88-1.25). Considering that the study of siblings may decrease the potential effects of genes and environment, we believe that the result from siblings is more reliable. Therefore, stress-related disorders may not be associated with an increased risk of autoimmune disease among individuals with a history of other mental disorders.

Second, Song and colleagues found that the persistent use of selective serotonin reuptake inhibitors (SSRIs) was associated with a decreased risk of autoimmune disease among patients with posttraumatic stress disorder (PTSD) during the first year after diagnosis. However, these results must be further...