Biological Psychiatry: Celebrating 50 Years

Infections, Anti-infective Medications, and Suicidal Behavior: An Association Bearing Further Investigation

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Deliberate self-harm, encompassing suicide attempts, completed suicides, and nonsuicidal self-injurious behavior, is a global public health problem with a particularly strong impact on the world's youth and young adults. In the United States, suicide is the third leading cause of death among children 10 to 14 years of age and the second leading cause of death among adolescents and adults 15 to 34 years of age (1). Suicide attempts far outnumber completed suicides, and the personal, social, and economic costs of suicidal behavior are staggering. Suicidal acts impact not only the individual but also family, friends, and colleagues, a network that may number in the hundreds, and total lifetime medical and work-loss costs related to suicidal behavior are estimated to be in the tens of billions of dollars in the United States (1). Especially troubling is the fact that rates of both completed suicide and emergency department visits for self-harm have experienced a marked rise over the first 2 decades of the 21st century, with half of all states reporting a >30% increase in the suicide rate between 1999 and 2016 (2).

The emotional and economic burdens posed by suicidal behavior and the challenges faced in translating scientific knowledge into effective strategies for suicide prevention make it an important area for innovative research. One intriguing hypothesis is the theory that inflammation and infection may play a causal role in triggering and perpetuating mental illness and uniquely contribute to suicidal behavior. Rates of depression are estimated to be higher among individuals with illnesses characterized by neuroinflammation, including autoimmune disorders such as multiple sclerosis and lupus, and viral infections such as hepatitis C and human immunodeficiency virus (3). Higher rates of suicidal behavior have been observed in these chronic illness populations, as well as among individuals with histories of transient (influenza type B) or latent (*Toxoplasma gondii*) infections (3). Chronic or acute immune processes (e.g., illness, injury, and stress) induce an inflammatory cytokine response that may in turn modulate monoamine and tryptophan metabolism and induce dysregulation of the hypothalamic-pituitary axis (3). While much of the data regarding the relationship among infection, inflammation, and suicidal behavior have come from small cross-sectional studies, recent epidemiologic studies also support this association. In 2016, Lund-Sorenson *et al.* (4) found an increased risk of death by suicide after hospitalization for serious infection in a large population-based Danish cohort.

In the current issue of *Biological Psychiatry*, Gjervig Hansen *et al.* (5) extend Lund-Sorenson *et al.*'s work (4) to report on the relationship between less serious infection and a broad range of suicidal behavior. Drawing on Danish registry data, Gjervig Hansen *et al.* (5) followed 1.3 million youths and young adults over a period of up to 18 years (1995–2013), tracking individuals between 10 and 36 years of age. Using redeemed prescriptions for anti-infective agents as a proxy for mild to moderate infections, they compared individuals exposed to anti-infective agents with a reference group exposed only to topical antibiotics or penicillin. Deliberate self-harm—defined by a self-harm diagnosis recorded in any medical or psychiatric clinical setting and encompassing both suicide attempts and nonsuicidal self-injury—was considered the primary outcome; death by suicide was also examined.

While death by suicide was quite rare, deliberate self-harm was reported in about 1% of the sample; treatment with an anti-infective agent was common (5). Youth and young adults with infections treated with anti-infective agents were found to have an increased risk of self-harm (hazard rate ratio = 1.80 [95% confidence interval = 1.68–1.91]) (5). The risk of deliberate self-harm was higher as the number of redeemed prescriptions increased and greatest during the year after the last anti-infective prescription was filled, suggesting a time-sensitive dose–response relationship (5). Hospitalization for infection and the use of broad-spectrum antibiotics were also associated with higher hazard rate ratios for self-harm, suggesting that illness severity may differentially impact suicidal behavior. No association was noted between the use of anti-infective agents and completed suicide (5). Forty-seven percent of those who engaged in suicidal behavior carried a previous mental disorder diagnosis, suggesting that patterns of association between mental illness and self-harm may be similar in Denmark and the United States, where recent reports indicate that 46% of suicide decedents had a previously diagnosed mental health condition (2,5). In the Danish sample, rates of self-harm were much higher among those with mental disorders than among those without mental disorders, but sensitivity analyses suggest similar dose–response patterns of association between the number of filled prescriptions and self-harm in those with and those without mental disorders (5).

These results are intriguing, but they raise many questions. First, what are the possible mechanisms by which the risk of deliberate self-harm is increased among youths and young adults with infections treated with anti-infective agents? Gjervig Hansen *et al.* (5) considered many classes of anti-infective agents used to treat a wide range of bacterial, viral, and fungal infections. Antibiotics, the anti-infective agent prescribed in the greatest number of exposures, appear to account for much of the observed association between prescription medication use and self-harm, with the highest hazard rate ratio reported for

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broad-spectrum antibiotic use (5). Antiviral, antiparasitic, and antimycotic agents were not associated with increased risk, although previous studies have linked both viral (e.g., influenza type B, human immunodeficiency virus, and hepatitis B) and parasitic (*T. gondii*) infections to suicidal behavior (3,5). Gjervig Hansen *et al.* (5) suggest several possibilities. The use of broad-spectrum antibiotics may indicate more severe illness, one that is perhaps more likely to trigger an inflammatory cytokine cascade and induce depressed mood or impulsive, aggressive behavior (5). Broad-spectrum antibiotics may also cause greater disruption to the gut microbiome. Believed to influence brain function and behavior via bidirectional autonomic and neuroendocrine networks, perturbations in the microbiome may play a role in depression, anxiety, and neurodevelopmental disorders (6). Perhaps it is not infection but rather the downstream effects of antibiotic usage that place individuals at increased risk deliberate self-harm? Attributing causality would certainly be a leap from the data at hand, but it is an interesting consideration in this age of high rates of antibiotic use and growing concerns about antibiotic resistance.

However, given that the majority of youths experience an infection and receive anti-infective treatment, perhaps the more tractable question is not "What is it about illness and anti-infective medication use that increases risk for self-harm?" but rather "What is it about the absence of infection or treatment that instills resilience?" Are these resilient youths healthier individuals who are less susceptible to illness, or are they less susceptible to infections' downstream inflammatory effects? Are they people who get sick but who do not present for medical care or people who decline anti-infective treatment when ill?

Of course, it is possible that anti-infective prescriptions serve not only as a proxy for infection but also as a proxy for care-seeking behavior. Survey data suggest that many suicide attempts go unreported—perhaps as many as 55% of attempts among American young adults 18 to 25 years of age (7). Those who do not seek medical treatment for infections may also be less likely to present for care after engaging in self-harm behaviors. On the other hand, estimates suggest that approximately one quarter of youths and young adults who die by suicide had contact with a primary care provider in the month before death, and more than 60% had contact within the previous year (8). Contact with a primary care doctor may reflect help-seeking behavior for physical or mental health issues, somatic manifestations of psychological distress, or an etiologic role of infection or anti-infective use.

Regardless of the reason, the findings reported by Gjervig Hansen *et al.* (5) speak to the role that physicians' offices, emergency departments, and hospitals may play in the prevention of deliberate self-harm. In 2016, the Joint Commission recommended that health care systems screen all patients for suicidal ideation, and initial studies suggest that these screening programs, when operating with appropriate infrastructure and support, do not place undue burdens on health care workers or systems and successfully identify individuals who were not previously known to be at risk for self-harm (9). Among children presenting to the emergency department with mental health complaints, the Ask Suicide Screening Questions, a four-item screener, has shown excellent sensitivity and fair specificity in predicting return visits for suicidal behavior (10), and its use in the pediatric outpatient medical setting is currently under study (ClinicalTrials.gov identifier: NCT02830334). The increased risk for self-harm following treated infections in youths observed by Gjervig Hansen *et al.* (5) suggests that pediatricians and family physicians may want to consider sick visits as a time to screen for suicidal behavior, while mental health clinicians may want to be mindful of infection in the youths they treat. Mechanistic biologically based research to elucidate the link between infection, anti-infective medications, and risk for self-harm, as well as systematic efforts in health care settings to identify individuals at risk for self-harm and intervene, are needed.

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Article Information

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