

Anxiety and Depression: Linkages with Viral Diseases

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ABSTRACT

Anxiety and mood disorders are common in the general population in countries around the world. This article provides a review of the recent literature on anxiety and depressive disorders with a focus on linkages with several important viral diseases. Although the majority of studies have been conducted in developed countries such as the United States and Great Britain, some studies have been carried out in less developed nations where only a small percentage of persons with mental illness receive treatment for their condition. The studies summarized in this review indicate that there are important linkages between anxiety and depression and viral diseases such as influenza A (H1N1) and other influenza viruses, varicella-zoster virus, herpes simplex virus, human immunodeficiency virus/acquired immune deficiency syndrome, and hepatitis C. Additional studies are needed to further clarify the mechanisms for interactions between mental health and communicable diseases, in order to assist patients and further prevention and control efforts.

Keywords: Acquired immune deficiency syndrome; acute respiratory distress syndrome; generalized anxiety disorder; influenza A virus, H1N1 subtype; hepatitis C; major depression; varicella-zoster virus

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INTRODUCTION

Accounts of mental health and infectious diseases date to antiquity. Scientific appreciation for the many complex linkages between common anxiety and mood disorders and viral infectious diseases has rapidly

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expanded only in recent decades.¹⁻³ Infectious diseases and mental health conditions are now recognized to constitute among the largest categories of disease burden globally.¹ In this article I review recent literature on anxiety and mood disorders with a focus on linkages with several important viral diseases that affect adults and children in countries around the world. Although the majority of studies have been conducted in developed countries such as the United States and Great Britain, some studies have been carried out in less developed nations where only a small percentage of persons with mental illness receive treatment for their condition.^{1,4} In interpreting the public health relevance of published studies, it is important to consider whether the scientific findings are from low or middle income countries or from high income countries.¹ Of course, important barriers to care can exist even in high income countries.¹

The viral diseases considered in this article are those most discussed in the literature, caused by influenza A (H1N1) and other influenza viruses, varicella-zoster virus, cytomegalovirus, herpes simplex virus, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), and hepatitis C.⁵ Depressive symptoms occurring in non-viral infectious conditions (e.g., syphilis, Lyme disease, malaria) and post-infectious conditions such as post-polio syndrome,⁶⁻⁸ the long-term sequelae of West Nile virus infection,^{9,10} and the relationships between autoimmunity and serious psychiatric conditions are beyond the scope of this review. This review also does not consider certain maternal and child health topics such as the relationship between maternal depressive symptoms and children's receipt of routine vaccination or other health care in the first few years of life.¹¹ In order to provide a framework for the discussion that follows, I begin with a brief overview of anxiety and mood disorders.

OVERVIEW OF ANXIETY AND MOOD DISORDERS

Anxiety and mood disorders are among the most common mental health conditions in the general populations of countries around the world.¹ This is true in both low and middle income countries and in high income countries. Anxiety and mood disorders include generalized anxiety disorder, acute anxiety disorder, post-traumatic stress disorder (PTSD), phobias, panic disorder, major depressive disorder, bipolar illness, and other mood disorders. Other anxiety disorders include obsessive-compulsive disorder, and somatization disorder. Estimates of the prevalence of these anxiety and mood disorders are available from the National Comorbidity Survey Replication and the World Health Organization World Mental Health Surveys.^{12,13}

As noted in the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders, 4th Edition, Text Revision (DSM-IV), generalized anxiety disorder is characterized by persistent and excessive anxiety and worry over a period of at least six months.¹⁴ Symptoms of this disorder include restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and sleep disturbance. Acute stress disorder occurs within four weeks of a traumatic event and is characterized by symptoms similar to those seen in PTSD.¹⁴ The DSM-IV is currently under revision; diagnostic criteria for psychiatric conditions are periodically revisited and revised.

Symptoms of PTSD can develop after an individual experiences a severe traumatic event involving threatened death, serious injury, or witnessing an event that involves serious injury or death of another person, and responds with intense fear, helplessness, or horror. Thus, it is not just the nature of the exposure (e.g., being hospitalized in an intensive care unit for acute respiratory distress syndrome), but how the person experiences the traumatic event.¹⁵ Examples of extreme stressors include combat experiences, physical or sexual assault, exposure to a natural disaster such as a major earthquake or life-threatening pandemic, or being held as a prisoner of war or in a concentration camp. Symptoms of PTSD may include nightmares, intrusive thoughts or other re-experiencing phenomena, the avoidance of situations that remind the person of the traumatic event, a feeling of numbness or being socially detached from family and friends, and hyper-vigilance or hyper-arousal (e.g., feeling irritable or having difficulty concentrating).

Major depressive disorder is characterized by one or more major depressive episodes with five or more symptoms of depression such as depressed mood, loss of interest or pleasure in all or most daily activities, significant weight loss or gain, sleeping disturbances, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, or recurrent thoughts of death or suicidal ideation.¹⁴ The key feature of major depressive disorder is a period of at least two weeks during which there is either depressed mood or a loss of interest or pleasure in all or nearly all activities. For a diagnosis of major depressive disorder to be made, the symptoms must cause significant distress or impairment in social, occupational, or other areas of functioning, and not be due to a general medical condition or medication.¹⁴ Major depressive disorder may be mild, moderate, or severe; severe depressive disorder may occur with or without psychosis. The International Classification of Diseases (ICD) 10th revision includes separate codes to indicate whether the current episode of recurrent depressive disorder is

mild, moderate, severe without psychotic symptoms, or severe with psychotic symptoms.¹⁶ The 11th version of the ICD is now being developed through a collaborative process.¹⁶ The DSM-IV mirrors the ICD-10 for depression.¹⁴

FRAMEWORKS FOR UNDERSTANDING LINKAGES BETWEEN ANXIETY AND DEPRESSION AND VIRAL DISEASES

Previous authors have proposed frameworks for accounting for the influence of depression on the progression of HIV³; for understanding relationships among psychological trauma, PTSD, and health outcomes^{17,18}; and for identifying possible mechanisms for interactions between mental conditions and other health conditions including communicable and non-communicable diseases.¹ These frameworks highlight the importance of biological, personal, social, and cultural factors in understanding the linkages between mental conditions and important causes of morbidity and mortality. There are likely to be multiple biological and behavioral pathways that account for linkages between mental health conditions and viral diseases and the specific mechanisms can vary by viral illness. Mental conditions such as major depression can delay help-seeking or reduce the likelihood of detection of other health conditions including communicable diseases.¹ Depression and psychological stress have been shown to have a number of biological effects including reduced cell-mediated immunity and increased inflammatory processes.³ A further issue is that some viral diseases can directly affect the brain and result in mood disorders or cognitive impairment.¹

INFLUENZA VIRUSES

Influenza in endemic, annual or periodic pandemic forms is a major factor in morbidity and mortality globally. Vaccination is an important public health strategy for reducing risk of influenza at the population level, but there is individual variation in the level of protection afforded by vaccines.^{19,20} This variation may be partly accounted for by individual differences in exposure to psychological stress or stress-related psychological conditions. Evidence from animal and clinical studies suggests that stress-induced dysregulation of the immune system, which occurs through neuroimmune mechanisms (e.g., the hypothalamic-pituitary-adrenal axis), can be sufficient to reduce immune responses to vaccines for

influenza and other vaccine-preventable illnesses.¹⁹⁻²¹ Pedersen et al.¹⁹ conducted a meta-analysis of 13 studies that examined the impact of psychological stress on antibody responses following influenza vaccination. Significant negative associations were observed between psychological stress and antibody responses to vaccination.¹⁹ The authors did not comment on whether their findings were likely to be clinically significant. Few studies have examined the association between (reactive) depression and immune response to influenza vaccination. A recent systematic review of the literature on influenza and depression found insufficient evidence to conclude that patients with depression have a higher risk of influenza.²²

In addition to neuroimmune pathways, there may be additional mechanisms that account for linkages between stress, anxiety, and influenza, especially for novel influenza viruses that may be associated with increased morbidity and mortality. Population surveys conducted in several countries around the world examined behavioral reactions among members of the general public to the 2009-2010 influenza A (H1N1) pandemic.²³⁻²⁶ The surveys, which examined a variety of factors including state anxiety (i.e., a temporary emotional condition characterized by apprehension, tension, and fear about a particular situation or activity), were conducted to obtain information related to health risk communication and public adoption of measures to delay viral spread (e.g., hand and respiratory hygiene, voluntary isolation of symptomatic persons, and other social distancing measures). State anxiety (as opposed to trait anxiety and psychological anxiety disorders) may have a positive impact on public adoption of preventive measures.²⁴⁻²⁶ For example, persons with higher state anxiety scores have been reported to be more likely to practice hand and respiratory hygiene during an influenza pandemic.

There are additional linkages between influenza and anxiety disorders that pertain only to severe viral pneumonia such as cases of acute respiratory distress syndrome (ARDS) related to severe influenza A (H1N1).²⁷ Initial studies of patients admitted to intensive care units for treatment of severe influenza A (H1N1) reported mortality rates from 15-40 percent.²⁷ In a study of one-year outcomes among French patients who had been treated in intensive care units for H1N1-associated ARDS, Luyt et al.²⁸ found that the majority of the patients had symptoms of anxiety and depression as measured by the impact of event scale. Depression, anxiety, and PTSD have been associated with ARDS in several studies, which is consistent with the potentially life-threatening nature of the syndrome and associated morbidity.^{29,30} The trauma of being in an intensive care unit with ARDS is likely to result in PTSD in some individuals.

VARICELLA-ZOSTER VIRUS, CYTOMEGALOVIRUS AND HERPES SIMPLEX VIRUS

Primary infection with varicella-zoster virus (chicken pox) is a common disease of childhood which can lead to a chronic infection of the dorsal root ganglia.³¹ Several highly effective vaccines available since 1995 and recommended for all children in the US and elsewhere since 1996 have resulted in marked reduction in mortality and hospitalizations for varicella. Reactivation and replication of the viral infection can occur during older adulthood as shingles, due to immunosuppressive diseases or treatments and age-related decline in varicella-zoster virus-specific T cell-mediated immunity.³² Stress and psychological distress may play a role in the onset of shingles among persons who have not been vaccinated for varicella-zoster virus.³¹⁻³³ In addition, it is possible that elderly persons who suffer from depression have a decreased immune response to zoster vaccine.³² In the Depression Substudy of the Shingles Prevention Study, a double blind, placebo-controlled vaccine efficacy trial that was coordinated by the U.S. Department of Veterans Affairs, a measure of varicella-zoster virus cell-mediated immunity was found to be significantly lower among 52 subjects with major depressive disorder than in 52 age- and sex-matched controls who had no history of depression or mental illness.³² In addition, the severity of depression was inversely correlated with the severity of depressive symptoms.³² Among some persons who experience shingles, persistent pain due to postherpetic neuralgia can occur for months or years after the shingles have healed. Postherpetic neuralgia has been associated with depression and sleep difficulties.³¹

Cytomegalovirus and herpes simplex virus are considered below since the viruses are similar and there have been relatively few studies of possible linkages with anxiety and depression. The paucity of studies makes it difficult to use a weight-of-the evidence approach to assess the causality of the associations. Phillips et al.³⁴ examined whether infection with cytomegalovirus, a beta-herpesvirus, is associated with anxiety and depression in a community-based sample of 137 older adults in England. The majority of the participants (66%) were cytomegalovirus-seropositive and seropositive status was not associated with anxiety or depression.³⁴ Within the cytomegalovirus-seropositive group, however, persons with higher cytomegalovirus-specific antibody titres were more likely to be anxious or depressed. The authors noted that cytokines released in response to cytomegalovirus infection may moderate affect.³⁴ The direction of possible causal relationships is more difficult or impossible to determine from cross-sectional data.

Few studies have examined possible associations between depression and herpes simplex virus infection or reactivation. Miller et al.³⁵ found that antibody titres to herpes simplex virus, cytomegalovirus, and Epstein-Barr virus were associated with depressive symptoms among 65 patients with coronary artery disease.³⁵ Studies of adolescents and adults have found that depressed persons are more likely to engage in risky sexual behavior that places them at risk of sexually transmitted infections such as herpes simplex virus type 2 (HSV-2).³⁶⁻³⁸ The relationship between depression and HSV-2 may be one of dual causation since sexually transmitted infections may trigger (reactive) depression in susceptible persons.³⁶ Psychological stress has been associated with activation of HSV-2.³⁹

HUMAN IMMUNODEFICIENCY VIRUS

A sizeable number of studies have examined post-traumatic stress disorder (PTSD), depression, and other mental health conditions in HIV positive persons. Of particular interest are studies conducted following the introduction of highly active antiretroviral therapy (HAART). Most but not all of these studies have been conducted in high income countries rather than low or middle income countries.

Post-traumatic stress disorder.

Studies of comorbid HIV/AIDS and PTSD have focused on a wide variety of demographic, cultural, and socioeconomic subgroups of diverse populations including women,⁴⁰⁻⁴² socioeconomically disadvantaged persons,^{43,44} gay men,⁴⁵ and adolescents and young adults in developed countries such as the US and Great Britain.⁴⁶ Other studies have focused on adults or children in African countries impacted by the AIDS pandemic.^{47,48} In the US, PTSD rates have been reported to be 10.4 percent to 42.2 percent in treatment seeking and convenience samples of patients with HIV/AIDS.^{41,49} Assessments of the generalizability of study findings should consider the gender or sex of study participants. Several factors may account for the co-occurrence of HIV/AIDS and PTSD and other anxiety and mood disorders such as major depression. These include the potentially traumatic nature of being diagnosed with a disease that is often perceived as life-threatening; the relatively high rates of traumatic exposures (physical assault, sexual trauma, or the sudden, unexpected death of a close family member or friend) that have been reported in studies of persons with HIV/AIDS; and patient perceptions of AIDS-related stigma.^{41,50}

Although PTSD may develop following an HIV/AIDS diagnosis, the reverse is also true as some persons suffering from PTSD, substance abuse, or other psychiatric illness are more likely to engage in risky behaviors including unsafe sex.⁵¹ Early life stressors such as physical abuse, sexual abuse, neglect, verbal violence, or witnessed violence have been positively associated with incident HIV infection in 13,274 US men who participated in the National Epidemiologic Survey on Alcohol and Related Conditions, 2004-2005.⁵² Women, children, and sexual minorities may be exposed to HIV as a result of sexual trauma.⁵³ Intravenous drug abuse is another important risk factor in many populations around the world.

Results from studies conducted in the US, Great Britain, South Africa, and other countries indicate that the co-occurrence of HIV/AIDS and PTSD results in special challenges for people living with HIV/AIDS and their health care providers, and that it is important to consider the ages, gender, sexual orientation, socioeconomic background, and culture of at-risk persons.² Studies have shown that many women living with HIV/AIDS have PTSD stemming from sexual or physical assault or other adverse life experiences. Katz and Nevid⁴¹ examined risk factors for PTSD symptomatology in a sample of 102 HIV positive women who were recruited from HIV treatment centers in the New York City metropolitan area. Factors found to be associated with PTSD symptoms included greater number of HIV-related physical symptoms, prior history of trauma, greater perception of stigma, and less social support. About 15 percent of the women in the study had probable PTSD and an additional 20 percent had subsyndromal PTSD based on PTSD Checklist scores,⁴¹ although the study was limited by the small sample size and possible selection bias. Young persons living with HIV/AIDS are another vulnerable group in society that is often subject to physical violence and other traumatic experiences. Martin and Kagee⁴⁷ examined the percentage of persons who met criteria for lifetime PTSD and HIV-related PTSD among 85 patients attending public health clinics in the Western Cape, South Africa who had been recently diagnosed with HIV. The rate of lifetime PTSD and incidence of PTSD considered to be HIV-related was 54.1 percent (95% CI, 43.6-64.3%) and 40 percent (95% CI, 30.2-50.6%), respectively. Sexual minorities including gay men are additional population subgroups that have been the focus of studies on PTSD and HIV/AIDS.

Taken overall, results from published studies indicate that several factors may increase vulnerability to PTSD or increase symptoms of the disorder among persons living with HIV/AIDS. The distress associated with PTSD symptoms can interfere with daily functioning and make it more difficult

for patients to sustain healthy behaviors such as physical activity, smoking cessation, avoidance of alcohol abuse, and safer sex practices.^{17,51} PTSD can also have an adverse effect on medication adherence. Studies have shown that PTSD symptoms can make it more difficult for persons living with HIV/AIDS to adhere to life-saving therapy over time. Researchers have noted that, in some persons facing HIV/AIDS-related life challenges, medication use may serve as a reminder of a traumatic diagnosis or treatment experience, and patients may avoid taking medications in order to avoid distressing thoughts about their illness or because of dissociation.^{53,54}

Although strict medication adherence is needed for HAART to be effective, studies have shown that some persons living with HIV/AIDS self-report low levels of adherence.^{2,55} PTSD has been associated with decreased adherence with HAART regimens and with the faster progression of HIV/AIDS.^{40,53,55-58}

Major depression

Depression affects about 20-30 percent of persons receiving HIV medical care.⁵⁹ Persons living with HIV who are effectively treated for their depression are more likely to adhere to antiretroviral therapy over time, with sustained virologic suppression, and to enjoy better health and improved quality of life.⁵⁹ Although rates of current and lifetime major depression have been reported to be higher among HIV-infected persons than in the general population, effective pharmacologic treatment and psychotherapy are available for depression in persons living with HIV.⁶⁰

Several factors may account for linkages between depression and HIV/AIDS.⁵⁹ In persons with more advanced HIV/AIDS, some depressive symptoms may be due to disease progression or to co-infection by hepatitis C virus (HCV).^{61,62} Neurocognitive dysfunction has been reported in HIV-infected persons and in those co-infected with HCV.⁶³ A further issue is that some antiretroviral medications have been reported to be associated with central nervous system toxicity and depression and disruption of sleep.⁶⁴

Social and behavioral factors are also important. Persons suffering from depression may be more apt to engage in risky sexual behaviors and be at greater risk of contracting HIV or other sexually transmitted diseases.⁶⁵ Among persons living with HIV, alcohol abuse and depression can co-occur.⁶⁶ Persons suffering from depression that is either clinically unrecognized or inadequately treated may be more apt to abuse alcohol or other substances or to have difficulties with medication adherence.³ Persons living with HIV need to adhere to treatment regimens and sustain healthy behavior over long periods of time. They may be more likely to miss

medical appointments if they suffer from depression.⁶⁶ Depression can act as a barrier to health-seeking behavior and access to antiretroviral therapy.⁶⁶

Persons living with HIV who perceive greater stigma are more likely to be depressed.⁶⁷ Interventions that lead to decreased stigma and increased social support for persons living with conditions such as HIV/AIDS and hepatitis C are likely to improve their wellbeing and quality of life.^{3,68}

HEPATITIS C VIRUS

A sizeable body of scientific evidence links depression and HCV infection. Evidence from clinical studies, post-mortem findings, and neuroimaging studies suggests that the association between depression and HCV infection is likely to be causal.⁶⁹⁻⁷⁵ The evidence includes studies of intravenous drug users and other populations at risk of both mood disorders and blood-borne viral infections as well as clinical trials of interferon-based treatment regimens for hepatitis C. Depression and fatigue are common, indeed usual, adverse effects of interferon often leading to patient withdrawal from treatment. Depression in patients with chronic HCV infection can be a psychological response to a chronic progressive medical condition or to drug use.⁷⁰ People with cirrhosis, adenocarcinoma of the liver, or other complications of HCV may be more likely to have depression. Some persons living with hepatitis C experience depression, fatigue, or cognitive dysfunction, which cannot be explained by drug abuse or hepatic encephalopathy, although the effects of HCV on neurocognitive functions are generally mild.⁷¹⁻⁷⁴ Viral receptor molecules are expressed at the surface of blood- brain barrier endothelial cells and HCV may increase endothelial cell permeability.⁷⁵ However, HCV replicates at lower levels in endothelial cells than in hepatocytes.⁷⁵

SUMMARY AND CONCLUSIONS

In this review, I summarized studies which indicate important linkages between anxiety and depression and viral diseases such as influenza A (H1N1) and other influenza viruses, varicella-zoster virus, herpes simplex virus, HIV/AIDS, and hepatitis C. Influenza A and varicella-zoster virus (but not HIV or hepatitis C) are largely preventable by vaccination. HIV/AIDS and hepatitis C are treatable conditions and effective measures for preventing new infections have been identified. Improved therapies for hepatitis C, including those that do not include interferon, are being tested in clinical trials.

For several of the associations identified in this review, the relation is likely to be one of mutual causation (e.g., HIV/AIDS resulting in depression and depression increasing risky behaviors that may lead to HIV infection). In this situation, the relationships imply both risk and susceptibility as well as cause and effect.⁷⁶ The World Health Organization has emphasized the relationships between depression and HIV/AIDS in countries around the world.⁷⁷ Nevertheless, for some of the viral illnesses considered in this review (e.g., cytomegalovirus), there is insufficient evidence to draw conclusions about the causality of associations with anxiety and depression. Assessments of causality must consider not only the weight of the evidence but also possible biases such as uncontrolled confounding. The linkages between viral illnesses and mental health conditions reviewed in this article highlight potentially important avenues for disease prevention and control efforts, areas for further research, and potential translational studies aimed at further improving public health (e.g., immunizations) and clinical interventions and access to treatment.^{1,2}

Although the majority of studies have been conducted in high income countries such as the US and Great Britain, some studies have been carried out in low or middle income nations where only a small percentage of persons with mental illness receive treatment for their condition. Additional studies are needed in low income countries and other underserved populations in order to support public health interventions and health policy making. Some important infections discussed in this review are preventable by immunization. Although causal relationships are not yet established the discussed co-morbidity patterns provide additional reasons to promote routine immunization. The topic requires additional studies to further clarify the mechanisms for interactions between mental health and communicable diseases, in order to assist patients and reduce morbidity and mortality and improve quality of life.

Acronyms List:

ARDS = Acute respiratory distress syndrome

DSM-IV = The American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders, 4th Edition, Text Revision

H1N1 = Influenza A virus, H1N1 subtype

HAART = Highly active antiretroviral therapy

HCV = Hepatitis C virus

HIV/AIDS = Human immunodeficiency virus/acquired immune deficiency syndrome

HSV-2 = Herpes simplex virus type 2

ICD = The International Classification of Diseases

PTSD = Post-traumatic stress disorder

Conflicts of Interest: None declared.

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