EXHIBIT 14

Facing page: Michigan Medicine Human Data and Biospecimen Release Committee Rubric.

An asterisk indicates a National Institutes of Health definition. The Michigan Medicine Human Data and Biospecimen Release Committee includes faculty and staff with a broad range of patient-related, clinical, research, legal, ethical, conflict-of-interest, technical, and industry-partnership expertise. Biweekly meetings involving use of a standardized checklist have enabled review of 70 projects over the past 12 months (approximately 3 projects per meeting). Types of data and biospecimens and actions that are exempted from the review process include summary data statistics without any individual-level data elements; "send-out" data or biospecimens intended for processing only when there are no third-party claims to the samples or derivatives; data or biospecimens generated during a clinical trial governed by our explicit study-specific research consents; and sharing of data or biospecimens with state or federal agencies or other academic medical centers. HIPAA denotes the Health Insurance Portability and Accountability Act, IRB institutional review board, PI principal investigator, and U-M University of Michigan.

ary research, how to manage known limitations regarding written informed consent as an indicator of effective communication, and how to handle selection bias owing to disparities created by the recruitment and consent process. More research, dialogue, and participant engagement are needed to achieve the correct balance between risk to individual participants and benefit to medical centers and society.

Disclosure forms provided by the authors are available at NEJM.org.

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Flattening the Curve for Incarcerated Populations — Covid-19 in Jails and Prisons

Matthew J. Akiyama, M.D., Anne C. Spaulding, M.D., and Josiah D. Rich, M.D.

Because of policies of mass incarceration over the past four decades, the United States has incarcerated more people than any other country on Earth. As of the end of 2016, there were nearly 2.2 million people in U.S. prisons and jails.[1] People entering jails are among the most vulnerable in our society, and during incarceration, that vulnerability is exacerbated by restricted movement, confined spaces, and limited medical care. People caught up in the U.S. justice system have already been affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and improved preparation is essential to minimizing the impact of this pandemic on incarcerated persons, correctional staff, and surrounding communities.

Populations involved with the criminal justice system have an increased prevalence of infectious diseases such as HIV and hepatitis C virus (HCV) infections and tuberculosis. Disparities in social determinants of health affecting groups that are disproportionately likely to be incarcerated — racial minorities, persons who are unstably housed, persons with substance use disorders or mental illness — lead to greater concentrations of these illnesses in incarcerated populations. Yet implementation of interventions to address these conditions is often challenging in correctional settings owing to resource limitations and policy constraints. Therefore, comprehensive responses that straddle correctional facilities and the community often need to be devised.

For example, HCV, which is the most prevalent infectious disease in incarcerated populations, is most commonly spread through

injection drug use. Transmission can be reduced using measures known to reduce high-risk behaviors, such as opioid agonist therapy and syringe exchange. Although much of the country has yet to implement these strategies in correctional settings, managing transitions in care to and from the community and providing such services to people after incarceration has a large impact. Similarly, we have learned that controlling infections such as HIV and HCV in correctional settings can have positive effects both in these settings and on surrounding communities, as a form of treatment as prevention.

Highly transmissible novel respiratory pathogens pose a new challenge for incarcerated populations because of the ease with which they spread in congregate settings. Perhaps most relevant to the Covid-19 pandemic, the 2009 H1N1 influenza pandemic exposed the failure to include jails in planning efforts. By the spring of 2010, vaccine was plentiful, yet most small jails never received vaccine, despite the presence of high-risk persons, such as pregnant women, and the increased risk of transmission among unvaccinated persons who spent time detained in close proximity to one another.[2]

"Social distancing" is a strategy for reducing transmission and "flattening the curve" of cases entering the health care system. Although correctional facilities face risks similar to those of community health care systems, social distancing is extremely challenging in these settings. Furthermore, half of all incarcerated persons have at least one chronic disease,[3] and according to the U.S. Department of Justice, 81,600 are over the age of 60, factors that increase the risk of poor outcomes of infection. With limited ability to protect themselves and others by self-isolating, hundreds of thousands of susceptible people are at heightened risk for severe illness.

To date, the Federal Bureau of Prisons and certain states and municipalities have opted to suspend visitation by community members, limit visits by legal representatives, and reduce facility transfers for incarcerated persons. To reduce social isolation and maintain a degree of connectedness for incarcerated people, some correctional systems are providing teleconferencing services for personal and legal visits. Irrespective of these interventions, infected persons — including staff members — will continue to enter correctional settings. By March 14, some U.S. correctional staff members had tested positive for SARS-CoV-2, and the first Covid-19 diagnosis in a detained person was announced on March 16. A recent SARS-CoV-2 outbreak among cruise-ship passengers and crew in Yokohama, Japan, provides a warning about what could soon happen in correctional settings.[4]

To operationalize a response for incarcerated populations, three levels of preparedness need to be addressed: the virus should be delayed as much as possible from entering correctional settings; if it is already in circulation, it should be controlled; and jails and prisons should prepare to deal with a high burden of disease. The better the mitigation job done by legal, public health, and correctional health partnerships, the lighter the burden correctional facilities and their surrounding communities will bear. We have learned from other epidemics, such as the 1918 influenza pandemic, that nonpharmaceutical interventions are effective, but they have the greatest impact when implemented early.[5]

Therefore, we believe that we need to prepare now, by "decarcerating," or releasing, as many people as possible, focusing on those who are least likely to commit additional crimes, but also on the elderly and infirm; urging police and courts to immediately suspend arresting and sentencing people, as much as possible, for low-level crimes and misdemeanors; isolating and separating incarcerated persons who are infected and those who are under investigation for possible infection from the general prison population; hospitalizing those who are seriously ill; and identifying correctional staff and health care providers who became infected early and have recovered, who can help with custodial and care efforts once they have been cleared, since they may have some degree of immunity and severe staff shortages are likely.

All these interventions will help to flatten the curve of Covid-19 cases among incarcerated populations and limit the impact of transmission both inside correctional facilities and in the community after incarcerated people are released. Such measures will also reduce the burden on the correctional system in terms of stabilizing and transferring critically ill patients, as well as the burden on the community health care system to which such patients will be sent. Each person needlessly infected in a correctional setting who develops severe illness will be one too many.

Beyond federal, state, and local

action, we need to consider the impact of correctional facilities in the global context. The boundaries between communities and correctional institutions are porous, as are the borders between countries in the age of mass human travel. Despite security at nearly every nation's border, Covid-19 has appeared in practically all countries. We can't expect to find sturdier barriers between correctional institutions and their surrounding communities in any affected country. Thus far, we have witnessed a spectrum of epidemic responses from various countries when it comes to correctional institutions. Iran, for example, orchestrated the controlled release of more than 70,000 prisoners, which may help "bend the curve" of the Iranian epidemic. Conversely, failure to calm incarcerated populations in Italy led to widespread rioting in Italian prisons. Reports have also emerged of incarceration of exposed persons for violating quarantine, a practice that will exacerbate the very problem we are trying to mitigate. To respond to this global crisis, we need to consider prisons and jails as reservoirs that could lead to epidemic resurgence if the epidemic is not adequately addressed in these facilities everywhere.

As with general epidemic preparedness, the Covid-19 pandemic will teach us valuable lessons for preparedness in correctional settings. It will also invariably highlight the injustice and inequality in the United States that are magnified in the criminal justice system. As U.S. criminal justice reform continues to unfold, emerging communicable diseases and our ability to combat them need to be taken into account. To promote public health, we believe that efforts to decarcerate, which are already under way in some jurisdictions, need to be scaled up; and associated reductions of incarcerated populations should be sustained. The interrelation of correctional-system health and public health is a reality not only in the United States but around the world.

Disclosure forms provided by the authors are available at NEJM.org.

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Blood Ties

Eliana V. Hempel, M.D.

The expansive window of the ICU room looks out over a gorgeous Sunday sunset. The room is pristine and organized. Monitors beep reassuringly. An incentive spirometer and a paper menu rest — comically, given the situation — on the bedside table. Everything in the room is familiar to me; I'm a doctor.

I've known him a long time, but the disheveled man before me with the hunted look in his eyes seems unfamiliar. His handkerchief makes repeated trips from his mouth to his lap, and each time his look of horror at the increasing amount of bright red blood intensifies. He can barely breathe, let alone talk, and the metallic smell of blood mingles with the smell of raw fear.

The screen behind me suddenly starts to glow, and a face appears: the tele-ICU physician. Backup. Thank goodness. Maybe he'll have some ideas. I spring into calm-doctor mode. I've done this countless times, faced emergencies with a calm exterior even as I wracked my brain for differential diagnoses, last-ditch treatment plans, and comforting words for

EXHIBIT 15

Open Letter to ICE from Medical Professionals Regarding COVID-19

Acting Director Matthew T. Albence
U.S. Immigration and Customs Enforcement
500 12th St. SW
Washington, D.C. 20536

Dear Acting Director Albence,

As concerned clinicians, we are writing this letter to urge U.S. Immigration and Customs Enforcement (ICE) officials to release individuals and families from immigration detention while their legal cases are being processed to prevent the spread of COVID-19 and mitigate the harm of an outbreak.

In light of the rapid global outbreak of the coronavirus disease 2019 (COVID-19), we want to bring attention to the serious harms facing individuals in immigration detention facilities under the custody of ICE. Health and Human Services Secretary Azar declared a public health emergency on January 31, 2020. As of March 13, 2020, there have been over 132,000 confirmed cases worldwide with nearly 5,000 deaths.

Conditions of Detention Facilities

Detention facilities, like the jails and prisons in which they are housed, are designed to maximize control of the incarcerated population, not to minimize disease transmission or to efficiently deliver health care. This fact is compounded by often crowded and unsanitary conditions, poor ventilation, lack of adequate access to hygienic materials such as soap and water or hand sanitizers, poor nutrition, and failure to adhere to recognized standards for prevention, screening, and containment. The frequent transfer of individuals from one detention facility to another, and intake of newly detained individuals from the community further complicates the prevention and detection of infectious disease outbreaks. A timely response to reported and observed symptoms is needed to interrupt viral transmission yet delays in testing, diagnosis and access to care are systemic in ICE custody. Further, given the patchwork regulatory system, it is unclear whether ICE or the county and state health departments are responsible for ensuring public health oversight of facilities.

For these reasons, transmission of infectious diseases in jails and prisons is incredibly common, especially those transmitted by respiratory droplets. It is estimated that up to a quarter of the US prison population has been infected with tuberculosis[1], with a rate of active TB infection that is 6-10 times higher than the general population.[2] Flu outbreaks are regular occurrences in jails and prisons across the United States.[3],[4] Recent outbreaks of vaccine-preventable illnesses including mumps, influenza, and varicella have similarly spread throughout immigration detention facilities. From September of 2018 to August 2019, 5 cases of mumps ballooned to nearly 900 cases among staff and individuals detained in 57 facilities across 19 states, a number that represents about one third of the total cases in the entire US in that time frame.[5] With a mortality rate 10 times greater than the seasonal flu and a higher R0 (the

average number of individuals who can contract the disease from a single infected person)[6] than Ebola, an outbreak of COVID-19 in immigration detention facilities would be devastating.

Risks of a COVID-19 Outbreak in Detention

Emerging evidence about COVID-19 indicates that spread is mostly via respiratory droplets among close contacts[7] and through contact with contaminated surfaces or objects. Reports that the virus may be viable for hours in the air are particularly concerning.[8] Though people are most contagious when they are symptomatic, transmission has been documented in absence of symptoms. We have reached the point where community spread is occurring in the United States. The number of cases is growing exponentially, and health systems are already starting to be strained. Social distancing measures recommended by the Centers for Disease Control (CDC)[9] are nearly impossible in immigration detention and testing remains largely unavailable. In facilities that are already at maximum capacity large-scale quarantines may not be feasible. Isolation may be misused and place individuals at higher risk of neglect and death. COVID-19 threatens the well-being of detained individuals, as well as the corrections staff who shuttle between the community and detention facilities.

Given these facts, it is only a matter of time before we become aware of COVID-19 cases in an immigration detention system in which detainees live in close quarters, with subpar infection control measures in place, and whose population represents some of the most vulnerable. In this setting, we can expect spread of COVID-19 in a manner similar to that at the Life Care Center of Kirkland, Washington, at which over 50% of residents have tested positive for the virus and over 20% have died in the past month. Such an outbreak would further strain the community's health care system. Considering the extreme risk presented by these conditions in light of the global COVID-19 epidemic, it is impossible to ensure that detainees will be in a "safe, secure and humane environment," as ICE's own National Detention Standards state.

In about 16% of cases of COVID-19 illness is severe including pneumonia with respiratory failure, septic shock, multi organ failure, and even death. Some people are at higher risk of getting severely sick from this illness. This includes **older adults over 60** and people who have **serious chronic medical conditions like heart disease, liver disease, diabetes, lung disease, and who are immunocompromised**. There are currently no antiviral drugs licensed by the U.S. Food and Drug Administration (FDA) to treat COVID-19, or post-exposure prophylaxis to prevent infection once exposed.

As such, we strongly recommend that ICE implement community-based alternatives to detention to alleviate the mass overcrowding in detention facilities. Individuals and families, particularly the most vulnerable—the elderly, pregnant women, people with serious mental illness, and those at higher risk of complications— should be released while their legal cases are being processed to avoid preventable deaths and mitigate the harm from a COVID-19 outbreak.

*This letter was written by physician members of the New York Lawyers for the Public Interest Medical Providers Network and Doctors for Camp Closure.

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[6] The R0 is the reproduction number, defined as the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection.
[7] Close contact is defined as—
a) being within approximately 6 feet (2 meters) of a COVID-19 case for a prolonged period of time; close contact can occur while caring for, living with, visiting, or sharing a health care waiting area or room with a COVID-19 case
b) having direct contact with infectious secretions of a COVID-19 case (e.g., being coughed on)
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EXHIBIT 16

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Pandemic Influenza and Jail Facilities and Populations

Persons processed into and through jail facilities in the United States may be particularly vulnerable during an influenza pandemic. Among other concerns, public health and corrections officials need to consider flow issues, the high turnover and transitions between jails and the community, and the decentralized organization of jails. In this article, we examine some of the unique challenges jail facilities may face during an influenza pandemic and discuss issues that should be addressed to reduce the spread of illness and lessen the impact of an influenza pandemic on the jail population and their surrounding communities. (*Am J Public Health.* 2009;99: S339–S344. doi:10.2105/AJPH.2009.175174)

Laura M. Maruschak, MA, William J. Sabol, PhD, R.H. Potter, PhD, Laurie C. Reid, MS, RN, and Emily W. Cramer, MS

AT YEAREND 2007, MORE than 7.3 million adults were under correctional supervision in prison, in jail, on probation, or on parole, accounting for about 3.2% of the adult population in the United States.[1] Prisons are confinement facilities run by state or federal correctional authorities and typically house sentenced felons. Jails are confinement facilities usually administered by local law enforcement agencies and typically house persons awaiting trial or sentencing or who have been convicted and sentenced to terms of less than one year. Probation is a nonconfinement sanction involving supervision in the community. Parole is supervision of offenders after release from prison. Of the adults under correctional supervision, thirty percent—or about 2.3 million—were held in prisons or jail facilities throughout the country. About 800 000 of the 2.3 million were held in the more than 3000 jail facilities nationwide. Although jails held fewer inmates than prisons at yearend 2007, over the course of the year jails had more than an estimated 13 million bookings.[2]

Persons held in correctional facilities in the United States have higher rates of infectious and chronic diseases, mental illness, substance dependency, and homelessness prior to jail booking, than the general public.[3] During an influenza pandemic, these health and socioeconomic issues would likely make jail inmates particularly vulnerable because of their compromised immune systems and possible diminished capacity to understand the importance of taking medication. In addition, the large number of jail facilities and high turnover of jail inmate populations would likely present challenges for managing the spread of infection into jails from surrounding communities and, equally important, from jails into communities.

Such possibilities suggest the need for jail facilities and public health officials to work together during the pandemic influenza planning process. However, the decentralized nature of the jail system in the United States complicates the planning process. In this article, we address characteristics

of jails that public health officials need to be aware of when planning for an influenza pandemic. These characteristics include

1. the number and varying size of jail facilities in United States,
2. the high turnover of jail populations,
3. the connection between jail facilities and their surrounding communities,
4. the capacity of jails as it pertains to the ability to handle infected inmates, and
5. the prevalence of and capacity to provide services for physical health, mental health, and substance abuse problems of inmates.

We used data and reports collected and compiled by the United States Bureau of Justice Statistics (BJS), a component of the United States Department of Justice that is dedicated to collecting, analyzing, publishing, and disseminating data on crime, criminal offenders, victims of crime, and the operations of justice systems at all levels of government. The BJS data provide the only nationally representative data on jails and jail inmates. Because of the number and variety of jail systems in the nation, this is an important issue, though often overlooked. We focused on those data relevant to pandemic planning, such as population characteristics, turnover, and comorbid medical conditions. In addition, we reviewed 2005–2009 pandemic influenza planning literature posted by the government (available at http://www.pandemicflu.gov).

LOCAL JAIL CHARACTERISTICS

The latest data available indicate that throughout the United States, more than 3200 jail facilities were distributed among 2860 jail jurisdictions.[4,5] Jail jurisdictions are locally—usually county—operated entities. The majority of jails are likely to be operated by a county Sheriff, though some are operated by county governments and a small number are operated by private corporations under contract from a county government. Some local governments have formed regional jails, facilities created to house inmates from several counties. Conversely, some large counties maintain more than one jail facility.

Although most counties have a jail, the jail inmate population is concentrated in large jurisdictions. At midyear 2008, there were about 786 000 inmates held in jails nationwide.[6] The roughly 1100 jails holding fewer than 50 inmates on an average day (38% of all jails nationwide) held only 3.0% of the jail inmate population. Conversely, the largest 170 jails, which averaged more than 1000 inmates per day, (and accounted for 6% of all jail jurisdictions nationwide) housed 52% of the nation's jail inmate population (Figure 1).

Regardless of size, most jails perform multiple roles in the community (see the box on page S342). Partly as a result of performing multiple roles, jails admit and release annually many more times the number of detainees than they hold on a given day. For example, during 2007 jails had an estimated 13 million bookings. These bookings did not represent unique individuals, however. The number booked during the 12 months ending June 30, 2007, was 17 times the size of the jail inmate population at midyear 2007.[2] Moreover, the high ratio of admissions to total jail populations indicates that the jail inmate population turns over rapidly. During the last week of June 2007, jail turnover nationwide—measured in terms of the total number admitted and released divided by the average population—was 63.5%. This turnover varies with jail size. During the last week of June 2007, smaller jails—those housing fewer than 50 inmates on average—turned over at more than 100%, whereas the turnover rate in the largest jails—housing more than 1000 inmates—was about 54%.[2]

The high turnover rate also implies that the average time spent in jails is comparatively short. Nationwide, the average time served in jails amounts to approximately 21 days.[6] By comparison, average time served in prisons is more than 2 years. In the largest jails, almost half of all inmates booked into them spend 2 or fewer days there. A BJS survey covering the largest 140 jails in 2004 found that approximately 46% of the inmates released from these jails during 2004 served fewer than 3 days, another 16% served 3 to 7 days, and 18% served between 1 week and 1 month. At the time of release, only 1% of those from the largest jails had served more than 1 year.[7] Also in these large jails, the number of admissions fluctuates monthly, indicating that there may be some seasonality to the turnover rate. For example, within the largest jails, monthly admissions from January 2003 to January 2004 fluctuated from a low of 308 582 in February to a high of 357 259 in August.[2]

In terms of managing the movements of inmates booked into their facilities, jail administrators have relatively little control over the flow of inmates entering their facilities or the rate at which they leave. Judges decide whom to detain prior to trial and whom to sentence to jail rather than prison. Detained inmates may make bail at any time and be released. Parole boards or probation officials determine which offenders to detain in jail while awaiting hearings to determine if there were violations of conditions of supervision. Offenders regularly move from community supervision into jail facilities and from jail facilities into community supervision. On any given day, half of the nation's jail population represents failure to comply with conditions under community supervision—not necessarily a new criminal act. For example, during 2004 approximately 219 000 parolees (up from 133 900 in 1990) and 330 000 probationers (up from 222 000 in 1990) failed to comply with the conditions imposed on them while under community supervision and were returned to incarceration, either in prison or in jail.[7]

Despite the volatility in jail population movements over time, jail capacity has expanded at about the same rate, or even slightly faster, than the increase in the number of inmates confined in jails. Nationwide at midyear 2008, the number of inmates held in jails amounted to 95% of rated capacity. Since 2002, jails nationwide have operated at between 93% and 95% of capacity, up slightly from 90% in 2001. Smaller jails—for example the roughly 1100 housing fewer than 50 inmates on average and holding 3% of the jail population nationwide—operated at 67.3% of capacity. The 350 largest jails—those housing more than 500 inmates on average and holding more than two thirds of jail inmates nationwide—operated at near 100% of capacity.[5]

Many of the inmates flowing through jails suffer from medical and mental health conditions. In

2002, more than one third (37%) of all jail inmates reported having a current medical problem. Some 14% of jail inmates reported multiple medical problems. The most frequently reported medical problems by jail inmates were chronic diseases. The most commonly reported medical problem was arthritis (13%), followed by hypertension (11%), asthma (10%), and heart problems (6%). Infectious diseases were reported less frequently; approximately 4.3% reported ever having had tuberculosis, 2.6% reported hepatitis, 1.3% reported HIV infection, and 0.9% reported an STD.[8,9]

Wilper et al. provide standardized estimates of the prevalence of common chronic conditions in the incarcerated population (both prison and jail) as a whole for the purposes of comparing the prevalence of these conditions with those found in the general population. For our article, comparisons to the general population are not as relevant as the overall percentage of jail inmates with conditions.[9]

In addition, an increasing number of persons held in jails are non-US citizens, many of whom may come from high-risk countries. At midyear 2007, about 39 000 jail inmates were non-US citizens, accounting for about 5% of the jail population. Since 2000, the number of non-US citizens being held in jails has increased by 40%, whereas the number of US citizens being held in jails increased 9%.

Substance abuse and mental health problems are more prevalent among jail inmates than are medical problems. Approximately 2 in 10 jail inmates reported a recent history of mental health problems, including a clinical diagnosis or treatment in the year before arrest or since admission, according to a BJS survey of jail inmates.[10] Further, a recent study by Steadman et al., in which clinical diagnostic instruments were used to determine past-month prevalence of serious mental illness among a sample of adult male and female jail inmates in 5 jails (2 in Maryland and 3 in New York), reported a prevalence of serious mental illness of 14.5% for males and of 31.0% for females.[8] In addition, many inmates exhibit symptoms of mental health disorders based on criteria specified in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), as nearly two thirds (64%) of jail inmates reported either a recent history of a mental health problem or symptoms of a mental health disorder.

Among jail inmates in 2002, two thirds (68%) met the criteria for either dependence on or abuse of alcohol or other illegal substances. Over half (53%) of jail inmates were either dependent on or abusing drugs, and nearly one half (47%) were either dependent on or abusing alcohol.[12] These factors combined affect issues of consent and ability to follow hygiene and prevention guidelines for inmates.

A review of personal interviews with jail inmates showed that in 2002, nearly half (47%) said that staff checked them to see if they were sick, and 81% said staff asked them questions about their health or medical history at admission.[8,11] More than 4 in 10 jail inmates had a medical examination since admission. Of every 10 inmates, 6 had been tested for tuberculosis, and more than 2 in 10 had been tested for HIV. About 4 in 10 jail inmates with a then-current medical problem had seen a doctor.

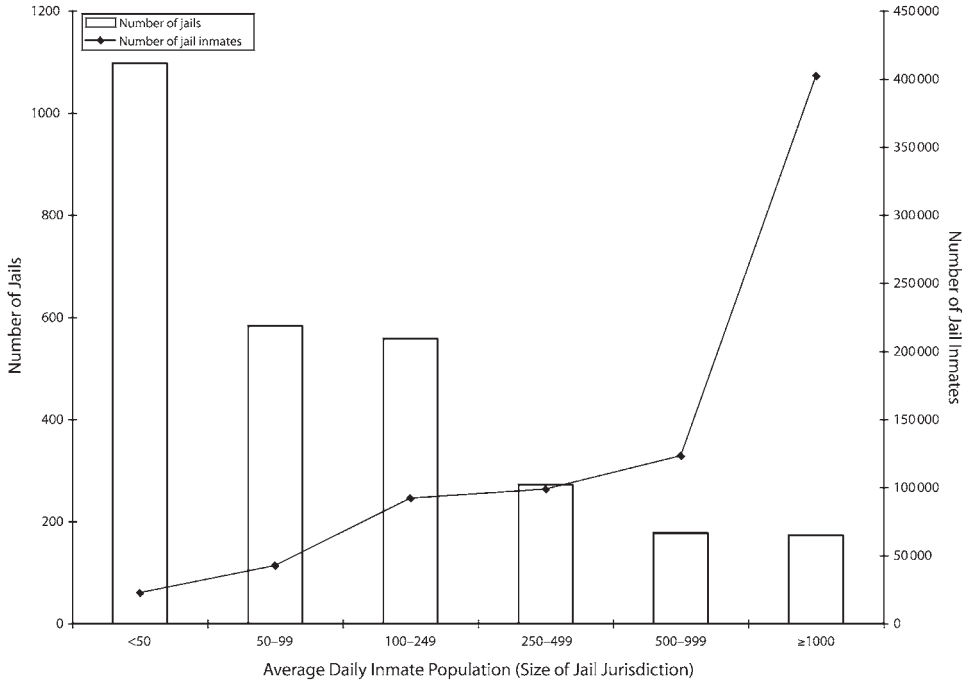

FIGURE 1—Number of jail inmates and jail jurisdictions, by size of jail jurisdiction: midyear 2007

IMPLICATIONS

The number and varying size of jails, the high turnover in jails, the connection between jails and the community, the capacity of jails, and the prevalence of and capacity to provide services for physical health, mental health, and substance abuse problems all have implications for preparing for pandemic influenza.

Although standards do exist for infection control programs in jails, only around 350 jails nationwide, less than 10% of all jails, are accredited by either or both major accrediting bodies with health standards (though this does not include states with internal accrediting processes). Good infection control practices inside jails may have an immediate effect on surrounding communities, and jails may be similarly affected by good infection control practices in communities. Yet given the fluidity of

Roles of Jails in Their Communities

Jails:

Receive individuals pending arraignment and hold them awaiting trial, conviction, or sentencing.
Readmit probation, parole, and bail bond violators and absconders.
Detain temporarily juveniles pending transfer to juvenile authorities.
Hold mentally ill persons pending their movement to appropriate mental health facilities.
Hold persons for the military, for protective custody, for contempt, and for the courts as witnesses.
Release convicted inmates to the community upon completion of sentence.
Transfer inmates to federal, state, or other authorities.
House inmates for federal, state or other authorities because of crowding in other facilities.

jail inmate populations, implementing infection control policies within jails may not be as easy as it sounds. In the largest jails, more than two thirds of the inmate population turns over within one week; in the smallest jails, the entire population turns over within one week. The short turnover times pose huge challenges in implementing infection control practices, particularly when jails are required to maintain security, transport detainees to court for hearings, and hold offenders for sentencing. The ongoing business of managing a jail poses challenges for administrators—adding procedures to control infection must take into account the roles and responsibilities of jails in the criminal justice system.

The pathway for transmission of pandemic influenza between jails and the community is a two-way street. Jails process millions of bookings per year. Infected individuals coming from the community may be housed with healthy inmates and will come into contact with correctional officers, which can spread infection throughout a facility. On release from jail, infected inmates can also spread infection into the community where they reside. Thus, a jail facility's pandemic influenza plan can directly affect not only the health of its inmate population but also the health of the surrounding community. For planning purposes, it is important to keep in mind that persons serving probation sentences are typically not eligible for health care in the community, in contrast to those held in jail. Further, while the Advisory Committee on Immunization Practices recommends providing influenza vaccine to all persons who want to reduce the risk of becoming ill with influenza or transmitting it to others, experiences with recent vaccine shortages raise questions about the priority that would be given to jail inmates and jail employees as vaccine recipients in the event of a pandemic.

Because jail capacity has expanded at approximately the rate of growth of the jail inmate population and it is not clear that a pandemic influenza outbreak would necessarily result in an increase in the number of persons held in jails, it is not obvious that expansion of jail capacity would be necessary during a pandemic. More important than the number of beds, per se, is the use of the bed. Important to the utilization of jail capacity for public health purposes is understanding the way in which people become sick with influenza. Influenza is thought to spread primarily from person to person when infected persons cough, sneeze, or talk, sending respiratory droplets into contact with susceptible persons. Research suggests that transmission might also occur when people touch contaminated objects and then touch their own nose, mouth or eyes with their hands.[13]

In the absence of a widely available pandemic influenza vaccine, corrections authorities could be constrained to recommend nonpharmaceutical interventions to reduce contact between people and to limit potential transmission. Planners would then need to consider developing infection control plans that specify needed reallocation of space and regrouping of inmates (possibly designated quarantine areas and treatment areas for those infected). If space and resources for delivery of medical treatment cannot be allocated, planners must think about security and staffing issues that could arise from the need for inmates to be transferred to hospitals. A primary function of jails is to transport inmates to court for appearances and back to jail, and jail administrators maintain security within facilities while operating these transport functions. However, in the event of an outbreak that resulted in a large increase in the number of inmates transferred to hospitals in addition to courts, jail managers will have to plan for the effects of additional transport to hospitals. Potentially, if expansion of jail capacity is needed, it may be expansion of the number of correctional officers to handle increased demands for transporting inmates and to avoid leaving facilities understaffed. The infection control planners should fully explore infection control measures that jails, employees, and inmates can take to prevent spread of influenza-like illness while still allowing the correctional facility to protect the community from offenders and ensuring the rule of law.

The data on morbidity in jails indicate that jail inmate populations contain many individuals with a compromised immune system. This factor may facilitate the spread of infection. Although jails are able to provide limited medical care, their capacity for screening for medical and mental health problems appears to be greater than their capacity to provide care. Planning for a pandemic outbreak should consider the health screening role for jails. One approach would be to develop new instruments for screening and to use public health resources to assist in training and implementing screening procedures. But implementing strategies to prevent the possible spread of infection may be difficult to put into practice unless a jail facility is able to screen and group its inmates according to infection status. Planners should consider developing and then exercising a workable, realistic plan to screen inmates and staff for influenza[14] using resources likely available during a pandemic.

Inmates with mental illness pose additional challenges for pandemic planning; even if inmates are screened and directed to resources in the community, health services will likely become overburdened

during a pandemic. Thus, any existing scarcity of mental health facilities in the community and any existing scarcity of access to necessary medications to control mental health illnesses may become more pronounced. This projected strain on health services poses a special challenge that planners need to address.

OTHER CONSIDERATIONS FOR PLANNING FOR PANDEMIC INFLUENZA IN JAILS

As corrections and public health officials align pandemic flu planning efforts with those of federal, state, local, public health, law enforcement, judiciary, and emergency management agencies, it is likely that their efforts would diminish the impact of a pandemic on correctional facilities and surrounding communities. The Department of Health and Human Services (HHS) provides a related and detailed pandemic planning checklist for correctional facilities at http://www.pandemicflu.gov/plan/workplaceplanning/correctionchecklist.pdf. Apart from drafting a plan, planners need to discuss their own missions and describe how they anticipate other agencies will respond during a pandemic. The Public Health/Law Enforcement Emergency Preparedness Workgroup (led by the Centers for Disease Control and Prevention and the Department of Justice) reported in July 2008 that law enforcement agencies and public health agencies should be aware of communication gaps that potentially exist between them. One example is that in the past, some agencies have mentioned other agencies in their plans and have made misguided assumptions about what actions those other agencies would implement. Another potential communication gap to address relates to the definition of key words such as "surveillance," which can have vastly different meanings between agencies; thus in advance of a pandemic, the group should ideally talk through and define words that have multiple meanings.[15]

An unresolved issue for planning is deciding which entities have responsibility for containing the spread of an influenza outbreak. One view is that testing and response should occur in jails and that the operations should be managed by jail officials. Another view is that public health officials should be primarily responsible for managing health concerns, including containing the spread of infection during a pandemic outbreak, whether done in jail facilities or in other locations in the community. Planning for pandemic influenza must address these issues of responsibility and delivery of services.

The Advisory Committee on Immunization Practices recommends providing influenza vaccine to all persons who want to reduce the risk of becoming ill with influenza or of transmitting it to others. The committee further advises an emphasis on providing routine vaccinations annually to certain groups at higher risk for influenza infection or complications, including all persons 50 years or older and other adults who are at risk for medical complications from influenza or who are more likely to require medical care.[13] The data on morbidity in jails indicate that jail inmate populations contain many persons with current medical problems. For planning purposes, when a pandemic influenza vaccine becomes widely available, each jail may want to compare the aforementioned Advisory Committee on Immunization Practices recommendations with their own inmate populations to see what percentage of the population would be most appropriate to vaccinate and in what order. In addition, given the high turnover in jail population and contact and interaction that correctional officers have with inmates, priority should be given to jail employees to minimize the spread of infection among them, which could in turn compromise prison security.

To ensure that jails can successfully carry out their missions during a pandemic, jail jurisdictions should plan for the likely absence of their employees due to the employee's illness or a family member's illness while at the same time working to protect employee health and to prevent spread of infection. Issues related to leave policies, health insurance, cross-training, and possible reduced work force are ideally addressed in advance of a pandemic. In addition to directing employees, planners should work to consider all the others who operate and who process through jails and who therefore during a pandemic could potentially be exposed to influenza.

We must begin to think of jails not as separate from the community but as collections of workers and detained persons who have a constant connection with the surrounding community. Thus, the boundary between jails and the community is relatively porous—what affects those behind the bars also affects those on the outside.

During a pandemic, jail medical services will likely be insufficient to treat large numbers of sick inmates; further, local hospitals may be overburdened and unable to admit inmates who are seriously ill with influenza.[16] Preventing the spread of pandemic influenza illness among inmates is therefore key to preserving the larger community's health. ■

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Contributors

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EXHIBIT 17

Sartorius N, Holt RIG, Maj M (eds): Comorbidity of Mental and Physical Disorders.
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Anxiety and Related Disorders and Physical Illness

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Abstract

Anxiety and related disorders are the most prevalent mental disorders in the general population. There is a strong bidirectional association between anxiety and related disorders and co-occurring general medical conditions. The co-occurrence of anxiety and related disorders and general medical conditions is associated with significant impairment, morbidity and economic costs. At the same time, recognition of anxiety and related disorders in people with medical illness may be challenging when comorbid with physical illness due in part to overlap in symptomatology. Furthermore, there is a relatively limited evidence base of randomized controlled trials in this population. Additional work is needed to improve screening for anxiety and related disorders in medical illness, to enhance diagnosis and assessment, and to optimize treatment.

Anxiety disorders, obsessive-compulsive and related disorders, and trauma- and stressor-related disorders are the most prevalent psychiatric disorders in the general population [1, 2], with generalized anxiety disorder the most common anxiety disorder in primary care populations [3]. Indeed, these anxiety and related disorders occur frequently with a range of general medical disorders [4, 5], including gastrointestinal disease [6], pulmonary disease [7, 8], cardiovascular disease [9], endocrine disorders [10], dermatological disorders [11] and cancer [12], as well as neuropsychiatric disorders such as chronic pain [13, 14], migraines [15], dementia [16] and Parkinson's disease [17]. In this chapter we review the epidemiology of comorbid anxiety and related disorders and physical illness, the growing evidence of a bidirectional relationship between these sets of conditions [18] and relevant randomized controlled trials in this area.

Epidemiology

Anxiety and related disorders are the most common psychiatric disorders worldwide, with a 12-month prevalence worldwide of between 4 and 20% [2]. The onset of anxiety and related disorders usually happens in childhood or adolescence, with many individuals first presenting with physical symptoms in primary care settings

Table 1. Common medical conditions associated with anxiety

Endocrine disorders	diabetes mellitus [32], thyroid disease [10], catecholamine-secreting pheochromocytoma
Gastrointestinal disorders	peptic ulcers [27], celiac disease [33], irritable bowel syndrome [26]
Musculoskeletal disorders	fibromyalgia/chronic fatigue syndrome [34], arthritis [35]
Neurological disorders	migraines [15], epilepsy, neurodegenerative illness [17]
Cardiorespiratory disease	asthma [30], angina [25], chronic obstructive pulmonary disease [7], mitral valve prolapse [36], cystic fibrosis [8], obesity [24, 37, 38]
Chronic pain	burns [14], cancer [12]
Infectious disease	HIV [39], tuberculosis [39]

[4]. Anxiety and related disorders are prevalent throughout life [19–22]. Furthermore, while the prevalence of comorbid anxiety and related disorders in those with chronic medical illness is not as well studied as depression in medical conditions, studies which have been done indicate it is as common [22–25]. A large cross-sectional study demonstrated that generalized anxiety disorder was the most prevalent anxiety disorder in primary care settings [3].

Systematic reviews have established that anxiety disorders are particularly prevalent in gastrointestinal disorders, pulmonary disease, cardiovascular disease, endocrine disease and cancer, as well as neuropsychiatric disorders such as chronic pain and migraines. In irritable bowel syndrome, up to 95% of patients have generalized anxiety disorder or panic disorder [26]. Similarly, panic disorder and generalized anxiety disorder were more prevalent in those with peptic ulcer disease [27]. In asthma, anxiety disorders occur in at least 25% of patients [28, 29]. In multiple studies of adolescents and adults with asthma, the prevalence of panic disorder and agoraphobia is almost three times that of the general population [30, 31]. Another anxiety disorder that co-occurs with respiratory illness is generalized anxiety disorder [31]. Table 1 outlines medical conditions associated with anxiety symptoms and disorders.

The co-occurrence of anxiety and general medical conditions is associated with significant impairment, morbidity and economic costs [36, 40–42]. For example, in a study of almost 500 medically ill persons diagnosed with anxiety disorders, those with posttraumatic stress disorder, panic disorder and social anxiety disorder were found more likely to be frequent consumers of healthcare, and to remain unable to maintain their roles and responsibilities, including work [43]. Medical comorbidities with anxiety disorders have also been shown to elevate suicide risk [44]. Adequate management of anxiety symptoms can improve outcomes of physical ill-health, and reduce the use of healthcare resources [4, 45]. In addition, some work suggests that quality of life and functional ability may be improved with optimal treatment of comorbid general medical and anxiety disorders [46–48].

Etiology

There is a growing body of evidence for a strong bidirectional association between anxiety and related disorders and co-occurring general medical

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conditions [14, 29, 49]. On the one hand, medical disorders may lead to fears about diagnosis, hospitalization, painful procedures and a foreshortened lifespan, while certain medical disorders may be linked physiologically to the development of anxiety and related disorders [50]. On the other hand, anxiety and related disorders may lead to vulnerability for various medical conditions. There may also be underlying factors that contribute to susceptibility for both anxiety disorders and physical conditions [51].

There is ongoing work to determine the precise nature of the relationships between anxiety disorders and physical illness in a number of areas. Thus, in irritable bowel syndrome, it has been suggested that infection or inflammation of the gastrointestinal tract lead to anxiety [29], while in asthma it has been postulated that increased partial pressure of carbon dioxide is responsible for panic attacks [52]. On the other hand, neurotransmitter disturbances and hypothalamic-pituitary-adrenal axis dysfunction have been postulated to play a key role in explaining how anxiety symptoms and disorders lead to medical illnesses [53].

The common underlying factors that may contribute to both anxiety disorders and comorbid physical illness have also received ongoing study. Genetic factors may, for example, predispose to both general medical conditions and anxiety disorders [54, 55]. In the World Mental Health Surveys, there were strong relationships between early adversity and subsequent onset of both anxiety disorders and various physical disorders, including chronic spinal pain, chronic headache, heart disease, asthma, diabetes and hypertension [56, 57].

Clinical Features

Recognition of anxiety disorders in people with medical illness can be challenging for several reasons. Firstly, anxiety symptoms are an understandable response to the diagnosis of medical conditions. A medical condition can be sufficient enough to be a stressor for an individual to develop an adjustment disorder, and in some cases even posttraumatic stress disorder. Secondly, anxiety symptoms may overlap with symptoms of an underlying medical disorder; thus, since patients with cancer may have insomnia and fatigue, conditions such as generalized anxiety disorder are overlooked. Similarly, medications used in the treatment of physical disorders may lead to anxiety symptoms [20, 49, 58].

In a patient with anxiety symptoms, a range of different diagnoses can be considered. Table 2 tabulates the main features of key anxiety and related disorders. Posttraumatic stress disorder is the anxiety and related disorder that is most commonly associated with gastrointestinal, cardiac, endocrine, chronic pain, migraines and Parkinson's disease [14, 22]. Symptoms of generalized anxiety disorder arguably most closely resemble those of many general medical conditions, particularly in the older population [20]. Panic disorder may, however, mimic a number of physical illnesses. Indeed, a broad range of different anxiety and related disorders have been associated with various physical illnesses.

Management

Early identification of anxiety symptoms and disorders in individuals with chronic illness is important in determining better outcomes for individuals with both sets of disorders [60–62]. The therapeutic alliance and collaboration between medical professionals may contribute to successful management of symptoms [50]. There is, however, a paucity of robust evidence in the treatment of chronically ill patients with comorbid anxiety and related disorders [51].

Cognitive behavioral therapy has been undertaken in a number of studies of individuals with medical illness and anxiety and related disorders. A systematic review of 32 psychotherapy

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Table 2. Anxiety and related disorders commonly seen in medically ill adult patients [14, 59]

Generalized anxiety disorder	characterized by a pervasive and excessive worry about everyday life events; this worry is difficult to control and is accompanied by somatic symptoms which impair the individual's functioning
Specific phobia	characterized by excessive, irrational and persistent fear of specific objects, situations or activities such as heights, flying and spiders
Social anxiety disorder	characterized by an intense and excessive fear of scrutiny and humiliation in social situations which then leads to avoidance of these situations, or development of panic attacks when the situations are endured
Panic disorder	characterized by recurrent unexpected panic attacks described as discrete events in which the individual experiences symptoms that peak within a few minutes and resolve spontaneously, coupled with anticipatory anxiety about future panic attacks
Posttraumatic disorder	a disorder in which the individual experiences a traumatic event; the disorder is then characterized by recurrent distressing re-experiencing phenomena, increased arousal, persistent avoidance of reminders and stimuli associated with the event, and negative cognitions and mood
Hypochondriasis	characterized by preoccupation with having a severe disease; the individual cannot be reassured despite medical investigations
Obsessive-compulsive disorder	characterized by recurrent intrusive distressing thoughts or images (obsessions) which are neutralized by some other thought or repetitive mental act/behavior (compulsions)
Substance/medication-induced anxiety disorder	characterized by anxiety symptoms which are directly related to the physiological effects of a substance or medication
Adjustment disorder with anxiety	characterized by a time-limited, maladaptive anxiety response to an identifiable stressor
Separation anxiety disorder	characterized by excessive, developmentally inappropriate anxiety upon separation of the child from the home or from significant attachment figures
Anxiety disorder not otherwise specified	diagnosed when the individual's symptoms are severe and distressing but do not meet diagnostic criteria for any other anxiety disorder

trials in patients with irritable bowel syndrome and anxiety disorders indicates the efficacy of cognitive behavioral therapy in reducing somatic distress [63–65]. A systematic review of 20 studies of cognitive-behavioral interventions in nearly 3,000 participants found that they may be effective in the management of HIV-/AIDS-associated anxiety [66]. Cognitive behavioral therapy has also been shown to reduce anxiety symptoms and distress in patients with cardiac disease and anxiety in one randomized controlled trial [67].

Behavioral strategies in anxiety disorders and comorbid medical illnesses include biofeedback, relaxation training and meditation [68, 69]. Two randomized controlled trials examining the effects of biofeedback in the management of asthma [69], and another two randomized controlled trials looking at relaxation therapy showed a reduction in the use of bronchodilator agents and improved quality of life [70].

Hypnotherapy and interpersonal therapy are other treatment modalities showing promise in the management of pain related to procedures for

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cancer therapies [71, 72], but rigorous studies are lacking in this area [14, 64].

In patients with physical illness and anxiety and related disorders, there are relatively few randomized controlled trials to guide treatment choices. Thus, medications should be selected based on studies of efficacy in anxiety disorders, and on minimizing adverse events and drug-drug interactions. The selective serotonin reuptake inhibitors sertraline, citalopram and escitalopram have relatively few adverse events and are safe in interaction with other agents [73]. The serotonin-noradrenaline reuptake inhibitors venlafaxine and duloxetine have the potential advantage of being beneficial for pain symptoms, but venlafaxine has the disadvantage of requiring blood pressure monitoring [74]. Drugs such as mirtazapine and the tricyclic antidepressants may be efficacious in the treatment of some anxiety disorders, but carry a significant side-effect profile and may have worrisome drug-drug interactions [74]. Benzodiazepines and sedative-hypnotic agents may be helpful for anxiety symptoms, but should be used cautiously due to concerns of dependence [6]. The second-generation antipsychotic quetiapine is anxiolytic at low doses, and is efficacious in the treatment of some anxiety and related disorders [50], but its metabolic, cardiac and autonomic side-effect burden should be taken into consideration.

Conclusion

Anxiety and related disorders are frequently comorbid with chronic medical conditions. There is growing understanding of the bidirectional relationships between these sets of disorders. Recognition can be delayed due to the similarity of primary anxiety symptoms and anxiety secondary to general medical conditions. Pharmacotherapy management can be effective, but clinicians need to be aware of the side-effect burden of psychotropics in medical conditions as well as potential drug-drug interactions. There is a growing database of studies of cognitive-behavioral therapy showing efficacy in individuals with anxiety disorders and comorbid medical illness. Further work is needed to improve screening for anxiety and related disorders in medical illness, to enhance diagnosis and assessment, and to optimize treatment.

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EXHIBIT 18

brain sciences

MDPI

Review

Bipolar Disorder and Immune Dysfunction: Epidemiological Findings, Proposed Pathophysiology and Clinical Implications

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Abstract: Bipolar disorder (BD) is strongly associated with immune dysfunction. Replicated epidemiological studies have demonstrated that BD has high rates of inflammatory medical comorbidities, including autoimmune disorders, chronic infections, cardiovascular disease and metabolic disorders. Cytokine studies have demonstrated that BD is associated with chronic low-grade inflammation with further increases in pro-inflammatory cytokine levels during mood episodes. Several mechanisms have been identified to explain the bidirectional relationship between BD and immune dysfunction. Key mechanisms include cytokine-induced monoamine changes, increased oxidative stress, pathological microglial over-activation, hypothalamic-pituitary-adrenal (HPA) axis over-activation, alterations of the microbiome-gut-brain axis and sleep-related immune changes. The inflammatory-mood pathway presents several potential novel targets in the treatment of BD. Several proof-of-concept clinical trials have shown a positive effect of anti-inflammatory agents in the treatment of BD; however, further research is needed to determine the clinical utility of these treatments. Immune dysfunction is likely to only play a role in a *subset* of BD patients and as such, future clinical trials should also strive to identify which specific group(s) of BD patients may benefit from anti-inflammatory treatments.

Keywords: bipolar disorder; inflammation; cytokines; depression; neuroprogression; cognition; N-acetylcysteine; infliximab; celecoxib; minocycline

1. Introduction

Bipolar disorder (BD) is a severe and persistent mental illness associated with significant morbidity and mortality. While numerous hypotheses have been proposed to explain the underlying patho-etiology of BD, the mechanisms sub-serving disease onset and progression remain largely unknown. More recently, immune dysfunction has been implicated in the patho-etiology of BD [1]. The hypothesis that immune dysfunction may be a mediator of disease progression in BD was first proposed by Horrobin & Lieb (1981) [2] who hypothesized that immune modulation may be a key mechanism of action in lithium's mood stabilizing effects. They further hypothesized that the relapsing-remitting nature of BD may be driven by the immune system, as seen in other relapsing-remitting inflammatory disorders, such as multiple sclerosis (MS) [2]. Since their hypothesis was proposed, numerous investigators have studied the interaction between BD and immune dysfunction [1,3–5].

The primary aim of the current review is to summarize and synthesize studies assessing the interaction between BD and immune dysfunction. Towards this end, we will summarize the following key areas: (1) epidemiological data revealing high rates of comorbidity between BD and inflammatory disorders; (2) cytokine studies showing increased central and peripheral levels of pro-inflammatory

molecules in BD compared to healthy controls; (3) proposed pathophysiological mechanisms sub-serving the inflammatory-mood pathway and (4) clinical implications of the interaction between BD and immune dysfunction, with a focus on repurposing anti-inflammatory agents in the treatment of bipolar depression.

Of note, the current review is not a systematic review, but rather narrative in nature, to provide a broad overview of the topic. A systematic review was not conducted given the breadth of the topic and vast number of studies on the various elements of the interactions between BD and inflammation. As such, the authors decided to focus on particularly relevant studies rather than exhaustively reviewing all published articles. The authors acknowledge that this approach is vulnerable to the presentation of a biased perspective; however, have attempted to present in an unbiased manner, highlighting areas of controversy and disagreement when needed.

2. Bipolar Disorder and Inflammatory Comorbidities

One potential indicator to suggest an interaction between BD and immune dysfunction is the high rates of inflammatory medical comorbidities in BD [6]. The association between BD and inflammatory comorbidities has been well established in numerous epidemiological studies; however, the direction of causality remains somewhat unclear. As shown in Figure 1a, immune dysfunction may be a common underlying cause of both BD and an inflammatory comorbidity in a given patient. Alternatively, BD may proceed the inflammatory condition or vice versa (Figure 1b,c). All three scenarios are observed in the BD population suggesting that the interaction is likely bidirectional in that immune dysfunction, BD and inflammatory comorbidities may be perpetuating each other as shown in Figure 1d [6]. Further, genetic and environmental risk factors for immune dysfunction may simultaneously increase the risk of developing both BD and other inflammatory comorbidities. Herein we summarize pertinent epidemiological findings showing the association between BD and inflammatory comorbidities.

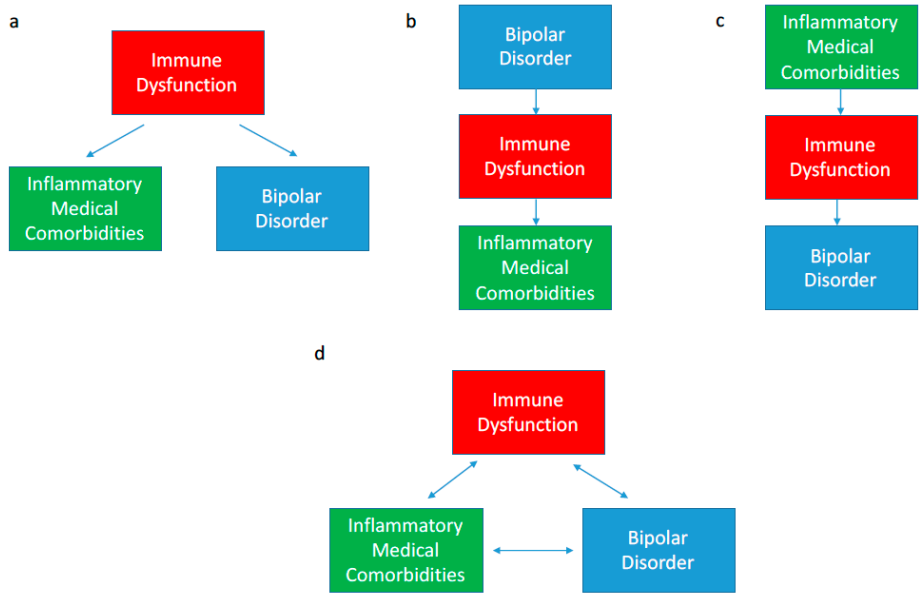

Figure 1. Potential interactions between bipolar disorder (BD), immune dysfunction and inflammatory comorbidities. (**a**) Immune dysfunction may be a common underlying cause of both BD and an inflammatory comorbidity; (**b**) BD may proceed the inflammatory condition or (**c**) vice versa. All three scenarios are observed in the BD population suggesting that the interaction is likely bidirectional in that immune dysfunction, BD and inflammatory comorbidities may be perpetuating each other (**d**).

When an inflammatory comorbidity is present, peripherally released pro-inflammatory cytokines may increase systemic cytokine levels (e.g., IL-2, IL-6, TNF-α) throughout the body, including in

the brain [7]. The subtler effects of chronic low grade systemic inflammation on off-target areas (e.g., the brain) has been increasingly recognized as important [8,9]. Admittedly, the association between BD and inflammatory comorbidities does not, in itself, prove causation, however, the biological mechanisms [10] to be further discussed in Section 4 provide further evidence that these epidemiological observations (summarized in Table 1) are likely to be more than just spurious associations.

Table 1. Inflammatory comorbidities associated with bipolar disorder, as shown by epidemiological studies.

Category	Specific Conditions
Autoimmune disorders	Inflammatory bowel disease (IBD) Systemic lupus erythematosus (SLE) Autoimmune thyroiditis Guillain-Barré syndrome (GBS) Autoimmune hepatitis Rheumatoid arthritis (RA) Multiple sclerosis (MS) Psoriasis
Chronic infections	Toxoplasma gondii (*T. gondii*), Possibly herpes simplex virus 1 (HSV1), cytomegalovirus (CMV) and human herpes virus 6 (HHV6)
Cardiovascular disease	Myocardial infarction Stroke Atherosclerosis Hypertension
Metabolic disorders	Type II diabetes mellitus
	Dyslipidemia
	Central obesity
	Metabolic syndrome
	Gout

2.1. Bipolar Disorder and Autoimmune Disorders

Autoimmune disorders represent the most "classic" of inflammatory conditions in that they are defined by the presence of immune dysfunction. In brief, autoimmune disorders occur when the immune system misrecognizes host tissue as pathogenic and attempts to remove the misidentified host tissue [11]. In doing so, both a local and systemic inflammatory response is initiated. Locally, the immune system attempts to break down and clear the triggering tissue (e.g., local break down of skin in psoriasis). While triggering this local inflammatory response, pro-inflammatory cytokines are released and circulated systemically with some degree of penetration to the central nervous system (CNS) as well. As a group, autoimmune disorders have been identified to occur at increased rates in BD [6]. Epidemiological studies have consistently shown increased rates of inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), autoimmune thyroiditis, psoriasis, Guillain-Barré syndrome (GBS), autoimmune hepatitis, MS and rheumatoid arthritis (RA) in BD [12–18].

2.2. Bipolar Disorder and Chronic Infections

Infections are also classically associated with both a local and systemic inflammatory response. The inflammatory response to infections is an essential physiological response that has been evolutionarily conserved amongst all mammal species [11]; however, in the case of chronic infections, the prolonged inflammatory response may also have deleterious effects, as the immune response is best suited for clearing an acute infection [19]. Similar to autoimmune disorders, chronic infections

may lead to chronic elevation of pro-inflammatory cytokines systemically and centrally. As such, an association between chronic infections and BD may be expected.

Dating back to the 19th century, there has been significant interest in the interaction between BD and chronic infections, such as Toxoplasma gondii (*T. gondii*), herpes simplex viru 1 (HSV1), cytomegalovirus (CMV) and human herpes virus 6 (HHV6); however, results have been mixed with poor replicability of identified associations [20]. The strongest replicated evidence has shown an increased co-prevalence of *T. gondii* in BD compared to the general population (odds ratio (OR) 1.52, $p = 0.02$) [21]. Interestingly, chronic infections, such as *T. gondii*, CMV and HSV1 have been associated with poorer cognitive function in BD [22,23]. Taken together, the association between BD and chronic infections remains unclear; however, BD patients with comorbid chronic infections may be at risk for a more severe phenotype secondarily to the presence of chronic low grade inflammation.

2.3. Bipolar Disorder and Cardiovascular Disease

Immune dysfunction is a key feature of cardiovascular disease (CVD) as inflammation plays a significant role in the progression of atherosclerotic plaques [24]. Cardiovascular disease has been strongly associated with BD in a bidirectional fashion. To emphasize the importance of this association, the American Heart Association (AHA) has recently recognized BD as an independent risk factor of early CVD. Indeed, replicated epidemiological studies have identified BD as an independent risk factor for CVD and vice versa [25–30]. Both cardiovascular and psychiatric researches have pointed to immune dysfunction as a likely key factor mediating this observed interaction. The high rate of comorbid BD and CVD is of particular importance because of its role in early mortality in BD; the increased prevalence of CVD is primarily responsible for the 10- to 20-year decrease in life expectancy in BD compared to the general population [31]. With this interaction in mind, some investigators have suggested that targeting immune dysfunction in this patient population may serve to simultaneously improve outcomes for BD, CVD and overall life expectancy [1,28].

2.4. Bipolar Disorder and Metabolic Disorders

Similar to CVD, immune dysfunction plays a key role in the progression of metabolic disorders [26,32,33]. Diabetes and central obesity have both been associated with chronic low grade inflammation, with the degree of inflammation being directly correlated with disease progression [34]. With immune dysfunction as a likely key mediating factor, BD has been strongly associated with increased rates of diabetes, obesity, dyslipidemia and metabolic syndrome [12,35,36].

A key factor facilitating chronic inflammation related to metabolic disorders is the presence of visceral adipose tissue (i.e., central obesity). Visceral adipose tissue is a direct source of chronic low-grade inflammation, increasing the production of pro-inflammatory adipokines and cytokines including IL-6, TNF-α, and C-reactive protein (CRP) [37,38]. Subcutaneous adipose tissue serves as a "metabolic sink" to prevent accumulation of visceral adipose tissue; however, under certain genetic (e.g., polygenic risk factors for central obesity) and environmental (e.g., sedentary lifestyle and poor diet) conditions, high volumes of dysfunctional visceral adipose tissue may accumulate [37,38]. In the context of chronic positive energy balance (e.g., greater caloric intake then expenditure), adipocytes undergo hypertrophy and have increased triglyceride stores [39]. The lypolytic rate is therefore increased leading to increased production of leptin (pro-inflammatory) and decreased production of adiponectin (anti-inflammatory), thereby signaling the release of pro-inflammatory cytokines [40]. Further, adipocyte hypertrophy promotes macrophage infiltration of adipose tissue. The resultant cross talk between macrophages and adipocytes promotes further release of pro-inflammatory cytokines and adipokines [37–40].

Bipolar disorder has also been associated with a slightly increased risk of developing gout [41]. With this epidemiological observation in mind, several investigators have recently hypothesized that purinergic system abnormalities and related variations of uric acid may be involved in the pathophysiology of BD [42,43]. Uric acid has been strongly associated with other metabolic disorders,

increased oxidative stress and inflammation [44,45]. Further, several proof-of-concept clinical trials have identified a potential anti-manic effect of drugs lowering uric acid (e.g., allopurinol) [46].

3. Cytokine Changes Associated with Bipolar Disorder

Cytokines are signaling molecules of the immune system which may increase or decrease local and systemic inflammatory responses. Measuring cytokine levels peripherally (i.e., serum levels) and centrally (i.e., cerebral spinal fluid (CSF) levels) provides insight into immune system activity. Cytokine levels can identify current levels of inflammation and identify which specific part of the immune system is over or underactive leading to the observed immune dysfunction in BD. Moreover, as signaling molecules, specific cytokines may be directly implicated in the pathophysiology of BD and may therefore present as potential novel targets of treatment.

Cytokine levels have significant fluctuations and variability; however, some trends have emerged through numerous cytokine studies of BD patients compared to healthy controls [3,4]. These cytokine studies have consistently shown elevated levels of pro-inflammatory cytokines in BD, suggestive of chronic low grade inflammation. Serum levels of pro-inflammatory molecules including interleukin-4 (IL-4), tumor necrosis factor alpha (TNF-α), soluble interleukin-2 receptor (sIL-2R), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), soluble receptor of TNF-α type 1 (STNFR1) and CRP are elevated in BD patients compared to healthy controls [3,47–49]. This cytokine profile indicates dysfunction of the *innate* immune system.

Another key observation has been variability in cytokine profiles depending on mood state (i.e., differing cytokine profiles during periods of depression, mania, hypomania and euthymia). This variability in cytokine profiles might suggest variable involvement of immune dysfunction in depression versus mania versus euthymia. Significant heterogeneity in BD cytokine studies has been problematic and, as such, there has been no clear cytokine profile that is reproducibly associated with each mood state [3,4]. This significant heterogeneity also suggests that inflammation is likely a pertinent pathogenic factor for only a *subset* of BD; this subset of BD may potentially represent an "inflammatory-BD" that may be pathophysiologically dissimilar from other BD patients. This potential sub-typing of BD is currently being investigated with important treatment implications.

Within the context of this substantial heterogeneity, the following mood-dependent cytokine profiles have been identified. The most robust evidence exists for an association between pro-inflammatory cytokines and depressive episodes, in both bipolar and unipolar depression [50]. During depressive episodes, serum levels of CRP, TNF-α, IL-6, IL-1β, sTNFR1 and CXCL10 are elevated [10,47,51]. Increased depression severity is associated with greater elevations of pro-inflammatory cytokines [52]. During manic episodes, serum levels of IL-6, TNF-α, sTNFR1, IL-RA, CXCL10, CXCL11 and IL-4 are often elevated [47,51]. During euthymic periods, sTNFR1 is the only consistently elevated inflammatory marker [47,48]. One significant limitation of these cytokine studies is their cross-sectional nature (i.e., serum levels are usually only taken at one point in time). Longitudinal studies are needed to measure cytokine levels within the same group of BD subjects to determine how they change during and in between mood episodes. Understanding this chronological relationship (e.g., if cytokines are elevated prior to versus after mood episode onset) would also provide further insight into the cross-talk between BD and immune dysfunction.

4. Pathophysiology of the Inflammatory-Mood Pathway

Numerous mechanisms have been identified which may mediate the bidirectional interaction between BD and immune dysfunction. Many of these mechanisms have been largely established in animal models [53]. More recently, clinical studies have provided evidence to suggest that these preclinical findings are valid in humans as well [10,54]. Herein we describe some of the key biological mechanisms which may contribute to the inflammatory-mood pathway. Of note, many of these mechanisms are not exclusive to BD and may trans-diagnostically sub-serve the interactions observed between immune dysfunction and other brain disorders (e.g., unipolar depression, schizophrenia,

neurodegenerative disorders) [55]. Currently, it remains unclear the degree of overlap versus divergence in inflammatory processes mediating the interaction between immune dysfunction and various neuropsychiatric disorders [56]. We hypothesize that there are likely both trans-diagnostically shared immune pathways as well BD-specific immune pathways (i.e., immune changes and mechanism that may not be present in other disorders).

Central to the inflammatory-mood pathway is the ability of peripherally circulating cytokines to traverse the blood-brain-barrier (BBB). Systemically circulating cytokines may traverse the BBB via active transport channels and through leaky regions of the BBB [57]. Of note, the relative permeability of the BBB for various cytokines remains unclear; however, replicated evidence has demonstrated clear associations between elevation of cytokines in serum samples (i.e., peripherally circulating cytokines) with the same cytokines being elevated in cerebral spinal fluid (CSF) samples (i.e., cytokine levels in the CNS), suggesting that likely all cytokines may penetrate the CNS to some degree [47]. Recent findings in animal models have also suggested the presence of lymphatic vessels in the brain which could provide another direct pathway for cytokines and other signalling molecules to enter the CNS [58]. Cytokines may then signal several downstream effects which alter the structure and function of key brain regions sub-serving mood and cognitive function. Cytokines can directly alter monoamine levels, cause over-activation of microglial cells and lead to increased oxidative stress in the brain [53]. The net effect of these changes is neurodegeneration and decreased neuroplasticity in key brain regions which may lead to the phenotypic changes observed in BD and other brain disorders.

4.1. Cytokine-Induced Neurotransmitter Changes

Monoamine changes have been the focus of mood disorder research for many years. Further, the majority of psychiatric medications' primary mechanism of action is through alteration of monoamine levels [59]. Pro-inflammatory cytokines may directly and indirectly alter monoamine levels in the CNS through numerous pathways. More specifically, TNF-α, IL-2 and IL-6 have been shown to directly alter monoamine levels [60]. IL-2 and interferon-gamma and alpha (IFN-γ and -α) increase the enzymatic activity of indolamine 2,3-dioxygenase (IDO), thereby increasing the breakdown of tryptophan to depressogenic tryptophan catabolites (TRYCATs). Serotonin (5-HT) levels may be further modulated through the IL-6 and TNF-α dependent breakdown of 5-HT to 5-hydroxyindoleacetic acid (5-HIAA) [61]. Depletion of tryptophan and decreased levels of 5-HT can directly impair affective and cognitive function [62].

Inflammation may also directly alter levels of dopamine and norepinephrine. Pro-inflammatory molecules, such as IFN, induce the activation of the guanosine-triphosphate-cyclohydrolase-1 (GTP-CH1) enzyme. Increased expression of GTP-CH1 results in the formation of neopterin and tetrahydrobiopterin (BH4), a cofactor used by phenylalanine hydroxylase (PH), tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH) to form tyrosine (Tyr), dopamine, norephinephrine, and serotonin, respectively; however, inflammation lowers pyruvoyl tetrahydropterin synthase (PTPS) activity, thus favouring neopterin formation instead of BH4 [63–65]. With decreased BH4 levels, the activity of PH, TH and TPH is decreased thus lowering the production of dopamine, norepinephrine and serotonin [55,66,67].

Taken together, pro-inflammatory signaling may decrease the levels of dopamine, norepinephrine and serotonin, which has long been associated with worsening mood and cognitive symptoms. Current pharmacotherapies target the end result of this pathway, namely, monoamine levels [59]. Targeting inflammation may have more disease modifying potential as immune dysfunction is "upstream" of the monoamine changes observed in mood disorders; correcting the underlying cause (i.e., immune dysfunction) may provide greater benefits than only treating symptomatically by correcting the downstream effect (i.e., monoamine changes).

Of recent interest has also been the potential interaction between inflammation and another key neurotransmitter, namely, glutamate. The importance of the glutamate system in mood disorder pathophysiology has been highlighted by the robust evidence demonstrating the rapid and

potent antidepressant effects of ketamine, an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist [68,69]. Significant cross-talk between glutamate and the immune system has now been demonstrated in pre-clinical and clinical models [70]. Inflammatory cytokines have been shown to influence glutamate metabolism through direct effects on microglia and astrocytes. As such, inflammatory cytokines may increase glutamate levels thus causing abnormal over-activation of glutamate receptors leading to uncontrolled increases of calcium influx through NMDA receptor channels, with the final result of excitotoxicity and impaired neuroplasticity [71].

The administration of exogenous pro-inflammatory cytokines has been shown to increase glutamate levels in the basal ganglia and anterior cingulate cortex (key brain regions sub-serving mood disorder pathology) as measured by magnetic resonance spectroscopy (MRS) [72]. Further, MRS studies in patients with unipolar depression have revealed that increased markers of inflammation (e.g., CRP) correlate with increased glutamate levels in the basal ganglia, which was specifically associated with anhedonia and psychomotor retardation [73]. In addition, an antidepressant response to ketamine may be predicted by elevated baseline inflammatory markers [74,75], further suggestive of significant cross-talk between immune dysfunction, the glutamate system and mood disorder pathophysiology.

4.2. Pathological Microglial Over-Activation

Microglia are the macrophages of the CNS that serve an important role in facilitating neuroplasticity [76–78]. Microglia aid in the pruning of unused neural circuits to allow for more space and energy to be made available for more frequently used neural circuits. Under physiological conditions, microglia may effectively prioritize the most important neural circuits leading to optimal brain structure and function [77,78]. However, with chronic inflammation, pro-inflammatory cytokines promote prolonged over-activation of microglia [76]. With this over-activation, microglia may aberrantly prune important neural circuits sub-serving mood and cognitive function (e.g., prefrontal cortex (PFC), amygdala, hippocampus, insula and the anterior cingulate cortex (ACC)) [76,79]. This process results in a positive feed-forward loop whereby activated microglia release cytokines, which further increases inflammation and further microglia recruitment and activation. The release of cytokines from activated microglia may also further perpetuate the previously discussed monoamine changes. Lastly, the over-activation of microglia increases the production of reactive oxygen species (ROS) leading to local oxidative stress, further damaging neural circuitry in key brain regions sub-serving mood and cognition [80]. This unfortunate cascade may contribute to the neuroprogression of BD as increasing numbers of important neural circuits are destroyed [47,81–83].

4.3. Inflammation and Increased Oxidative Stress

Oxidative stress has also been associated with mood disorders and is intimately connected with immune dysregulation, as inflammation increases oxidative stress and oxidative stress increases inflammation [84–86]. Oxidative stress occurs when there is an imbalance between the production of ROS and production of antioxidants responsible for neutralizing ROS [87]. Replicated evidence has demonstrated increased ROS and decreased antioxidants in BD, leading to pathologic neurodegeneration in key brain regions sub-serving mood and cognition [88–90]. Mood disorders have been associated with increased levels of pro-oxidant markers, namely, 8-hydroxy-2′-deoxyguanosine (8-OHdG), F2-isoprostanes, malondialdehyde (MDA) and decreased levels of anti-oxidant molecules, namely, glutathione (gamma-glutamyl-cysteinyl-glycine; GSH), superoxide dismutase (SOD) and glutathione peroxidase (GPx) [91]. Further, in unipolar depression, antidepressant response (to conventional antidepressants) has been associated with decreased oxidative stress, suggesting a mediational role of oxidative stress reduction in the effective treatment of mood disorders [87]. As such, there has been great interest in further understanding the mechanisms sub-serving increased oxidative stress along with the potential novel drug targets these mechanisms may offer.

4.4. Hypothalamic-Pituitary-Adrenal (HPA) Axis Over-Activation

Pro-inflammatory cytokines, namely IFN, TNF-α and IL-6, significantly up-regulate HPA activity thereby increasing systemic cortisol levels [92]. Under physiological conditions, HPA activation is advantageous to aid in the stress response required with an acute infection or injury. However, with chronic inflammation, HPA activation may be prolonged with deleterious effects related to chronic hypercortisolemia [93]. Additionally, chronic hypercortisolemia leads to downregulation of glucocorticoid receptor synthesis, translocation and sensitivity in the pituitary and hypothalamus, effectively inhibiting the negative feedback loop of the HPA axis [94]. This loss of the negative feedback loop leads to further propagation of hypercortisolemia with the well-established negative downstream effects (e.g., mood, cognitive and physical squealy) of chronically elevated cortisol levels [95–98]. Further, impaired cortisol suppression itself has long been recognized a strong predictor of mood disorders [98].

Dysfunction of the HPA axis has been identified in numerous medical and psychiatric disorders, however, the particular relevance in BD, in specific, was further emphasized by a recent meta-analysis and systematic review [99]. Belvederi Murri et al., (2016) identified forty-one studies showing that BD was consistently associated with significantly increased levels of cortisol (basal and post-dexamethasone) and adrenocorticotropic hormone (ACTH), but not of corticotropin-releasing hormone (CRH). These authors suggested that progressive HPA axis dysfunction is a putative mechanism that might underlie the clinical and cognitive deterioration of patients with BD and that targeting the HPA axis might be a novel strategy to improve the outcomes of BD [99].

4.5. The Microbiota-Gut-Brain Axis

In recent years, the role of the microbiota-gut-brain axis in neuropsychiatric disorders has become of great interest [100–102]. The gut and brain may communicate in a bidirectional fashion through numerous pathways including via the parasympathetic nervous system (primarily the vagus nerve), the gut neuroendocrine system, the circulatory system (delivering neuroactive metabolites and neuro-transmitters directly produced in the gut), and most notably, via the immune system [101]. The composition of the gut microbiota may have a large impact on the signaling molecules, including cytokines, that are being produced by the gastrointestinal (GI) system. The GI system may induce the production of pro-inflammatory cytokines on an acute or chronic basis. These cytokines may have direct effects on brain function as previously described.

Numerous investigators are questioning the potential impact of altering the gut microbiota on immune function and mental illness [103]. While this field is still in its infancy, the potential for novel treatments targeting the gut microbiota to treat BD may represent a completely new class of hypothesis-driven therapeutic interventions. For example, in a recent case report, Hamdani et al., (2015) suspected that a manic episode may have been triggered by alteration of the gut microbiota [104]. Given their hypothesis that the manic episode was triggered by perturbation of the gut-brain axis, the patient was treated with daily activated charcoal (a potent absorbent of gut inflammatory cytokines) instead of conventional anti-manic agents. The manic episode was successfully treated which corresponded to decreased serum levels of pro-inflammatory cytokines and chemokines. While targeting the microbiota to treat BD has yet to be assessed in any clinical trials, this case reports shows promise for a potential role of this novel target.

4.6. Inflammation and Sleep Dysfunction

Sleep dysfunction is a key feature of BD. During all phases of illness, changes in sleep patterns are commonly reported [105]. Indeed, during manic or hypomanic episodes, there is a characteristic decreased need for sleep. During depressive episodes, there may be difficulties achieving adequate quality or quantity of sleep or alternatively, hypersomnia in which patients are sleeping many more hours than would be typical for the general population. Even during euthymic periods, sleep

complaints are still common in BD [105]. Sleep dysfunction is also strongly associated with immune dysfunction. Replicated evidence has demonstrated sleep dysfunction to be associated with increased levels of pro-inflammatory cytokines with a bidirectional causal association identified [106,107]. As such, interest has grown in immune dysfunction as a potential nexus sub-serving the bidirectional interaction between sleep dysfunction and BD [108,109].

5. Clinical Implications

Currently available treatments for BD have poor long term outcomes with high rates of treatment resistance and relapse [110]. Additionally, tolerability is often poor with significant adverse effects, such as weight gain and insulin resistance, being common with most evidence-based treatments [111]. Given the significant interaction between immune dysfunction and BD, the immune system presents as a potential novel target in the treatment of BD. The evidence discussed above suggests that inflammation may play a direct effect in the pathophysiology of BD in a subset of patients. Therefore, repurposing anti-inflammatory agents in the treatment of BD may potentially have disease modifying effects by targeting the underlying etiological processes rather than only treating symptomatically (i.e., the current approach).

Several proof-of-concept clinical trials have assessed the antidepressant effects of anti-inflammatory agents in the treatment of both unipolar [112] and bipolar [113] depression. In a recent meta-analysis conducted by our group to evaluate the antidepressant effects of anti-inflammatory agents, we identified eight randomized clinical trials (RCTs) (n = 312) assessing adjunctive nonsteroidal anti-inflammatory drugs (n = 53), omega-3 polyunsaturated fatty acids (n = 140), N-acetylcysteine, (n = 76), and pioglitazone (n = 44) in the treatment of BD. The overall effect size of adjunctive anti-inflammatory agents on depressive symptom severity was −0.40 (95% confidence interval −0.14 to −0.65, p = 0.002), indicative of a moderate antidepressant effect with good overall tolerability [113]. The clinical applicability of this meta-analysis was limited by the small number of studies included and small pooled sample size; however, this analysis provided further proof of concept that targeting the immune system may be an efficacious novel treatment for BD. Herein we further summarize clinical trials assessing specific anti-inflammatory agents in the treatment of BD.

5.1. N-Acetyl-Cysteine (NAC)

Among all anti-inflammatory agents, NAC has the strongest evidence as an adjunctive treatment for bipolar depression [114,115]. In an RCT of NAC for BD (n = 75), adjunctive NAC was shown to lower depression severity scores throughout the trial with a statistically and clinically significant difference compared to conventional therapy alone at the primary endpoint of 24 weeks [114]. Additionally, post-hoc analysis of 17 participants from this sample who met criteria for a current major depressive episode (MDE) at baseline revealed that 8 of 10 participants in the NAC group had a clinical response (i.e., greater than 50% reduction in depression severity) compared to only 1 of 7 participant in the placebo group [116]. An eight-week open-label trial of NAC also showed antidepressant effects in BD [117]. The effect of adjunctive NAC in mania/hypomania was also explored in a small post-hoc analysis of 15 BD participants experiencing an acute manic/hypomanic episode comparing participants receiving adjunctive NAC (n = 8) versus adjunctive placebo (n = 7). This analysis revealed a greater improvement in symptoms of mania in the NAC group compared to placebo [118]. Overall, NAC shows promise as an adjunctive treatment for BD during all phases of illness; however, evidence is strongest for use in the acute treatment of bipolar depression.

5.2. Omega-3 Polyunsaturated Fatty Acids (Omega-3s)

Several RCTs have also evaluated the effects of adjunctive omega-3s, a naturally-occurring and well-tolerated anti-inflammatory agent [119]. Results have been mixed with some trials showing an antidepressant effect in BD [120,121] and others reporting no antidepressant effect compared to

conventional therapy alone [122–124]. When pooling these results together in a recent meta-analysis, a moderate and statistically significant anti-depressant effect of adjunctive omega-3s in BD was found compared to conventional therapy alone [119].

The mixed results of these studies assessing omega-3s in BD may suggest that omega-3s are beneficial in only a subset of BD. This hypothesis was further supported by a recent study assessing the antidepressant effects of omega-3s in the treatment of unipolar depression [125]. In this RCT, omega-3s were found to have a significant antidepressant effect in participants with elevated inflammatory markers. Intriguingly, in participants with normal cytokine levels, placebo had a greater antidepressant effect, compared to omega-3s, leading to an overall negative study outcome (i.e., no significant antidepressant effect was found when including the entire sample). While this study was in unipolar depression, it is likely that a similar effect may be observed in BD, in that only patients with elevated inflammatory markers may benefit from omega-3s, however, further study is still required to confirm or refute this hypothesis in the BD population.

5.3. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The anti-depressant effect of adjunctive NSAIDs has also been evaluated in BD. Nery et al., assessed adjunctive celecoxib in BD (n = 28) during an acute depressive or mixed episode [126]. Adjunctive celecoxib lowered depression severity by week 1; however, the primary outcome was negative as change in depression severity converged with the placebo group by the end of week 6. Saroukhani et al., assessed the effect of adjunctive aspirin in an RCT with male BD patients (n = 32) and found no significant difference between treatment groups by the primary endpoint of 6-weeks [127].

Three studies have also evaluated the effect of NSAIDs during acute manic/hypomanic episodes. In a small, proof-of-concept RCT, Arabzadeh et al., compared adjunctive celecoxib to treatment as usual for acute mania in BD inpatients (n = 46) [128]. They observed a significantly higher remission rate in the celecoxib group (87.0%) compared to the placebo group (43.5%) by the week 6 primary endpoint (p = 0.005). The same investigators also evaluated adjunctive celecoxib in an RCT of adolescent inpatients (n = 42) during an acute manic episode [129]. There was no significant difference in remission rates by the primary endpoint of 8-weeks, however, significantly greater improvement was observed in Young Mania Rating Scale (YMRS) scores in the celecoxib group compared with the placebo group by the week 8 primary endpoint (p = 0.04). In another RCT including BD inpatients (n = 35) with mania receiving electroconvulsive therapy (ECT), participants received either celecoxib or placebo from one day before the first ECT session throughout the sixth session. Brain-derived neurotrophic factor (BDNF) levels were also measured before and during the trial. Adding celecoxib was not associated with a significant rise in BDNF levels following ECT. No difference was noted between groups in terms of treatment response [130].

Taken together, the effect of NSAIDs in bipolar depression remains unclear as clinical studies have yielded mixed results. Additionally, adjunctive NSAIDs in the treatment of mania has yielded mixed results with anti-manic effects yet to be consistently demonstrated.

5.4. Minocycline

Minocycline is a tetracycline antibiotic with potent anti-inflammatory and neuroprotective effects [131]. Since the first case report of minocycline for bipolar depression was published in 1996 [132], there has been significant interest and off-label prescribing of minocycline for bipolar and unipolar depression; however, until this year (2017) there were no published RCTs to support or refute the antidepressant effects of minocycline. Recently, several open label trials and RCTs have been conducted to evaluate the antidepressant effects of minocycline for bipolar and unipolar depression [133–137]. In a recently published pilot, open-label, 8-week study, Soczynska et al., (2017) evaluated the efficacy, safety and tolerability of adjunctive minocycline for the treatment of bipolar I/II depression [134]. Adjunctive minocycline was associated with a significant reduction in depressive symptom severity from baseline to week 8 with overall good tolerability. While there has yet to be an

RCT of minocycline for bipolar depression, these results show promise for a significant antidepressant effect and merit further investigation.

5.5. TNF-α Inhibitors

TNF-α inhibitors have also been of interest as they may directly target a key cytokine (i.e., TNF-α) known to be implicated in the inflammatory-mood pathway. One pivotal RCT assessed infliximab in treatment resistant depression (n = 60), including both bipolar and unipolar depressed patients in their sample. Although the overall antidepressant effect was negative for this study, a significant antidepressant effect was observed for a subgroup of participants, namely, those with elevated levels of serum CRP and TNF-α [138]. Similar to the previously discussed omega-3 RCT [125], the results of this trial suggested that stratification using inflammatory biomarkers might help determine which patients may benefit from anti-inflammatory treatments. A 12-week RCT evaluating the effects of adjunctive infliximab for the treatment of BD patients with elevated inflammatory markers is currently underway, directly implementing this type of stratified approach (NCT02363738).

5.6. Anti-Inflammatory Effects of Conventional Mood Stabilizers

Also of interest has been understanding the relative impact of conventional mood stabilizers on the immune system. Indeed, as previously discussed, the initial hypothesis of conceptualizing BD as an immune disorder was developed through observing the immune-modulating effects of lithium, one of the oldest and most effective treatments of BD [2]. The interaction between lithium and the immune system is complex as lithium has been shown to have both anti-inflammatory (e.g., suppression of cyclooxygenase-2 expression, inhibition of IL-1β and TNF-α production, and enhancement of IL-2 and IL-10 synthesis) and pro-inflammatory effects (e.g., induction of IL-4, IL-6 and other pro-inflammatory cytokines synthesis) [139,140]. As such, the 'net effect' of lithium on immune function may vary greatly; however, long term lithium use has been associated with normalization of cytokine levels [141].

Compared to lithium, much less in know about the impact of valproic acid on the immune system. Pre-clinical studies have suggested possible anti-inflammatory effects of valproic acid, however, clinical studies have failed to demonstrate a significant anti-inflammatory effect, as determined by changes in cytokine levels pre- and post-treatment [142,143]. The impact of carbamazepine, lamotrigine and antipsychotics on the immune system also remains unclear due to a lack of clinical studies [141].

6. Conclusions

Bipolar disorder is strongly associated with immune dysfunction. Moreover, in a subset of BD, immune dysfunction is likely playing a key role in the pathophysiology of disease progression. The bidirectional interaction of BD with immune dysfunction is likely responsible for the high rates of inflammatory comorbidities, such as autoimmune disorders, cardiovascular disease and metabolic disturbances. This interaction is of particular importance as medical comorbidity is primarily responsible for early mortality in BD. Numerous biological mechanisms of the inflammatory-mood pathway have been identified that may present novel targets in the treatment of BD. Targeting the immune system shows promise for improving BD outcomes as it may allow for disease modification through treatment of the underlying etiology (i.e., immune dysfunction), rather than only superficially treating the downstream effects as symptoms arise. Numerous proof-of-concept clinical trials have demonstrated a positive effect of anti-inflammatory agents in BD with generally good tolerability. Currently available evidence suggests that anti-inflammatory agents may be specifically helpful in the treatment of bipolar depression. Conversely, the impact of anti-inflammatory agents in mania and hypomania remains unclear. Clinical studies have also suggested that anti-inflammatory agents may be only beneficial for a subset of BD patients, namely, patients with immune dysfunction, as indicated by elevation of inflammatory markers. As such, future clinical trials should stratify patients based on inflammatory profile to determine which specific anti-inflammatory agent(s) are efficacious in which specific subset of BD patients.

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EXHIBIT 19

ELSEVIER

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Depression and immune function
Central pathways to morbidity and mortality

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Abstract

Objective: The increased morbidity and mortality associated with depression is substantial. In this paper, we review evidence suggesting that depression contributes to disease and death through immune dysregulation. **Method:** This review focuses on recent human studies addressing the impact of depression on immune function, and the health consequences of those changes. **Results:** There is growing evidence that depression can directly stimulate the production of proinflammatory cytokines that influence a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, certain cancers, periodontal disease, frailty, and functional decline. Additionally, depression can down-regulate the cellular immune response; as a consequence, processes such as prolonged infection and delayed wound healing that fuel sustained proinflammatory cytokine production may be promoted by depression. **Conclusions:** These direct and indirect processes pose the greatest health risks for older adults who already show age-related increases in proinflammatory cytokine production. Thus, aging interacts with depression to enhance risks for morbidity and mortality.

Keywords: Proinflammatory cytokines; Interleukin 6; Psychoneuroimmunology; Stress

Depression is the most common psychiatric illness; both major depression and subthreshold depressive symptoms carry substantial health risks, reviewed in the articles in this issue of the journal and elsewhere [1–4]. Depression can affect health through many pathways; these influences may occur through health behaviors or compliance with medical regimens, as well as through alterations in the functioning of the central nervous system (CNS), immune, endocrine, and cardiovascular systems [5–8]. In this paper, we consider how depression may contribute to morbidity and mortality through immune dysregulation. We focus on a central immunological mechanism that serves as a gateway for a range of age-associated diseases, the dysregulation of proinflammatory cytokine production, particularly interleukin 6 (IL-6) [9].

Although we will not address the effects of disease on emotional distress in any detail, it is important to mention the bidirectional nature of the relationship. Unquestionably, cytokines have substantial effects on the CNS, including production and enhancement of negative moods, physical symptoms including lethargy and fatigue, and a range of sickness behaviors from shivering to loss of appetite [8,10,11]. Indeed, despite our focus on the impact of depression on immune responses and disease, there is also plausible evidence that the immune system has a role in the neuroendocrine and behavioral features of both depressive and anxiety disorders [8,11].

Morbidity, mortality, and aging: central immunological mechanisms

The immune system's inflammatory response can be triggered in a variety of ways, including infection and trauma. Inflammation is an important and constructive consequence of infection and injury; proinflammatory cytokines including IL-1, IL-6, and tumor necrosis factor (TNF) attract immune cells to the site of infection or injury, and prime them to become activated to respond. Anti-inflammatory cytokines such as IL-10 and IL-13 serve to dampen

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this immune response, including decreased cell function and synthesis of other cytokines. Thus, broadly speaking, cytokines provide intercellular signals that help to regulate the immune system's response to injury and infection.

Although the mechanisms associated with inflammation are critical to resolving infections and repairing tissue damage, chronic or recurring infections can provoke pathological changes [12]. For example, low levels of persistent inflammation may result when chronic infectious processes such as periodontal disease, urinary tract infections, chronic pulmonary disease, and chronic renal disease persistently stimulate the immune system. Persistent stimulation of proinflammatory cytokine production has the greatest impact among older adults who already show age-related increases in IL-6 production [13].

Depression and immune system alterations

Depression enhances the production of proinflammatory cytokines, including IL-6 [14–18]. Importantly, both depressive symptoms and syndromal depression are associated with heightened plasma IL-6 levels [16]. Following successful pharmacologic treatment, elevated IL-6 levels decline in patients with a major depression diagnosis [19]. Moreover, both physical and psychological stressors can provoke transient increases in proinflammatory cytokines [20–22]; in animal models, both stress and administration of epinephrine elevate plasma IL-6, consistent with evidence that IL-6 production is stimulated through β-adrenergic receptors, among other pathways [23,24]. Thus, production of IL-6 and other proinflammatory cytokines can be directly stimulated by negative emotions and stressful experiences, providing one direct pathway.

Overproduction of proinflammatory cytokines may lead to subsequent maladaptive immune and endocrine changes. IL-6 is a potent stimulator of corticotropin-releasing hormone (CRH) production, a mechanism that leads to heightened HPA activity, including elevated levels of plasma ACTH, followed by increased cortisol levels [14]; elevations in ACTH and cortisol can provoke multiple adverse immunological changes [8]. The complexity of these potential interactions is further underscored by one line of research which suggests that once cortisol levels rise, they can initiate, perpetuate or aggravate syndromal depression, depression-like behaviors, and depressive symptoms such as anxiety, insomnia, and poor memory [25]. Thus, negative emotions that dysregulate IL-6 secretion may also promote adverse neuroendocrine alterations.

Indeed, in addition to their association with enhanced secretion of proinflammatory cytokines, depression and distress can also have direct adverse effects on a variety of other immunological mechanisms, including the downregulation of cellular and humoral responses [8], and these changes are large enough to be clinically significant. For example, vaccine responses demonstrate clinically relevant alterations in immune responses to challenge under well-controlled conditions; accordingly, they serve as a proxy for response to an infectious agent [26–29]. More distressed and more anxious individuals produce immune responses to vaccines that are delayed, substantially weaker, and/or shorter lived [26–29]; as a consequence, it is reasonable to assume these same individuals would also be slower to develop immune responses to pathogens; thus, they could be at greater risk for more severe illness. Consistent with this argument, adults who show poorer responses to vaccines also experience higher rates of clinical illness, as well as longer lasting infectious episodes [30]. In addition, other researchers have shown that distress can alter susceptibility to cold viruses [31]. Furthermore, distress also provokes substantial delays in wound healing [32,33], and enhances the risk for wound infection after injury [34].

Increased susceptibility to infectious disease and poorer recovery from infection are substantial and important problems; in addition, however, they carry additional risks. Repeated, chronic, or slow-resolving infections or wounds enhance secretion of proinflammatory cytokines, a process that can serve to further inhibit certain aspects of immune responses (e.g., IL-2, a cytokine important in protection against infection) [35]. Thus, depression can directly affect the cells of the immune system and modulate the secretion of proinflammatory cytokines; in addition, depression may also contribute to prolonged or chronic infections or delayed wound healing, processes that indirectly fuel proinflammatory cytokine production. We next consider evidence which suggests that the etiology and course of a very broad range of diseases may be altered by dysregulated inflammatory responses.

Morbidity, mortality, and inflammatory immune responses

Inflammation has been linked to a spectrum of conditions associated with aging, including cardiovascular disease [9]. The association between cardiovascular disease and IL-6 is related in part to the central role that this cytokine plays in promoting the production of C-reactive protein (CRP), an important risk factor for myocardial infarction [23]. For example, high concentrations of CRP predicted the risk of future cardiovascular disease in apparently healthy men [36]. Further studies provided mechanistic links: chronic infections amplified the risk for development of atherosclerosis fourfold in subjects who were free of carotid atherosclerosis at baseline, conferring increased risk even in subjects lacking conventional vascular risk factors [37]. Indeed, the increased risk for artery-clogging plaque was greater than that conferred by elevated blood pressure or cholesterol [37]. Cardiovascular disease is the leading cause of death, and individuals with high levels of both IL-6 and CRP were 2.6 times more likely to die over a 4.6-year period than those who had low levels of both [38].

In addition to cardiovascular disease, inflammation has been linked to a spectrum of conditions associated with aging, including osteoporosis, arthritis, type 2 diabetes, certain lymphoproliferative diseases and other cancers (including multiple myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia), Alzheimer's disease, and periodontal disease [9]. In fact, more globally, chronic inflammation has been suggested as one key biological mechanism that may fuel declines in physical function leading to frailty, disability, and, ultimately, death [12,39]. For example, elevated levels of CRP and IL-6 predicted the development of type 2 diabetes in a 4-year follow-up period in healthy women after adjustments for BMI, family history of diabetes, smoking, exercise, alcohol, and hormone replacement therapy; among women in the highest vs. lowest quartiles, the relative risk for developing diabetes was 7.5 for IL-6 and 15.7 for CRP [40].

In other work, elevated serum IL-6 levels predicted future disability in older adults, a finding that may reflect the effects of the cytokine on muscle atrophy, and/or to the pathophysiologic role played by the cytokine in particular diseases [41]. Proinflammatory cytokines including IL-6 may slow muscle repair following injury and accelerate muscle wasting [42]; indeed, IL-6 and CRP also play a pathogenic role in a range of diseases associated with disability among the elderly (osteoporosis, arthritis, and congestive heart failure, among others) [41]. In this context, it is interesting that IL-6 is also associated with self-rated health [43], a robust predictor of mortality [10]. Thus, the clinical importance of immunological dysregulation for older adults is highlighted by increased risks across diverse conditions and diseases.

Health behaviors

In addition to the direct influences of psychological states on physiological function, distressed individuals are more likely to have health habits that put them at greater risk, including poorer sleep, a greater propensity for alcohol and drug abuse, poorer nutrition, and less exercise, and these health behaviors have cardiovascular, immunological, and endocrinological consequences [44]. Higher plasma IL-6 and CRP levels are associated with adverse health habits: values for both are higher in smokers than nonsmokers, in individuals who report less physical activity, and in those with a higher body mass index [39,41]. However, health habits including smoking, physical activity, and alcohol use have typically explained only a small part of the excess mortality associated with depression among older adults [3]. Similarly, IL-6 has robust relationships with morbidity and mortality, even after controlling for health behaviors [39–41]. Thus, health behaviors, although obviously important, are not sufficient to explain the relationship between depression and disease.

Pharmacologic treatments hold promise. A prospective trial of statins produced reductions in CRP, providing evidence that these drugs have anti-inflammatory effects in addition to their ability to lower lipids [45]. Additionally, the use of antidepressants can normalize activation of the inflammatory response system in patients with a major depression diagnosis [19]. The question of whether cognitive or other psychological treatments for depression have similar positive consequences is an important arena for future research.

Conclusions

Many lines of evidence now indicate that IL-6 may function as a "…global marker of impending deterioration in health status in older adults" (p. 645) [41]. Indeed, even after the point at which risk factors such as cholesterol, hypertension, and obesity predict health deterioration less successfully among the very old, chronic inflammation continues to be an important marker [41]. We have argued that depression (both syndromal and subsyndromal) directly prompts immune dysregulation, and these processes may lead to subsequent maladaptive immune and endocrine changes [14,20–24]. Production of IL-6 and other proinflammatory cytokines can be directly stimulated by depression, providing one direct pathway. In addition, depression and stress may also contribute to prolonged infection or delayed wound healing, processes that fuel sustained proinflammatory cytokine production. Thus, research that addresses the dysregulation of the immune and endocrine systems associated with depression could substantially enhance our understanding of psychological influences on health, particularly among the elderly.

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EXHIBIT 20

Stress Weakens the Immune System

Friends, relaxation strengthen health.

What the Research Shows

Stressed out? Lonely or depressed? Don't be surprised if you come down with something. Psychologists in the field of "psychoneuroimmunology" have shown that state of mind affects one's state of health.

In the early 1980s, psychologist Janice Kiecolt-Glaser, PhD, and immunologist Ronald Glaser, PhD, of the Ohio State University College of Medicine, were intrigued by animal studies that linked stress and infection. From 1982 through 1992, these pioneer researchers studied medical students. Among other things, they found that the students' immunity went down every year under the simple stress of the three-day exam period. Test takers had fewer natural killer cells, which fight tumors and viral infections. They almost stopped producing immunity-boosting gamma interferon and infection-fighting T-cells responded only weakly to test-tube stimulation.

Those findings opened the floodgates of research. By 2004, Suzanne Segerstrom, PhD, of the University of Kentucky, and Gregory Miller, PhD, of the University of British Columbia, had nearly 300 studies on stress and health to review. Their meta-analysis discerned intriguing patterns. Lab studies that stressed people for a few minutes found a burst of one type of "first responder" activity mixed with other signs of weakening. For stress of any significant duration - from a few days to a few months or years, as happens in real life - all aspects of immunity went downhill. Thus long-term or chronic stress, through too much wear and tear, can ravage the immune system.

The meta-analysis also revealed that people who are older or already sick are more prone to stress-related immune changes. For example, a 2002 study by Lyanne McGuire, PhD, of John Hopkins School of Medicine with Kiecolt-Glaser and Glaser reported that even chronic, sub-clinical mild depression may suppress an older person's immune system. Participants in the study were in their early 70s and caring for someone with Alzheimer's disease. Those with chronic mild depression had weaker lymphocyte-T cell responses to two mitogens, which model how the body responds to viruses and bacteria. The immune response was down even 18 months later, and immunity declined with age. In line with the 2004 meta-analysis, it appeared that the key immune factor was duration, not severity, of depression. And in the case of the older caregivers, their depression and age meant a double-whammy for immunity.

The researchers noted that lack of social support has been reported in the research as a risk factor for depression, an insight amplified in a 2005 study of college students. Health psychologists Sarah Pressman, PhD, Sheldon Cohen, PhD, and fellow researchers at Carnegie Mellon University's Laboratory for the Study of Stress, Immunity and Disease, found that social isolation and feelings of loneliness each independently weakened first-year students' immunity.

In the study, students got flu shots at the university health center, described their social networks, and kept track of their day-to-day feelings using a handheld computer (a new technique called "momentary ecological awareness"). They also provided saliva samples for measuring levels of the stress hormone cortisol. Small networks and loneliness each independently weakened immunity to a core vaccine component. Immune response was most weakened by the combination of loneliness and small social networks, an obvious health stress facing shy new students who have yet to build their friendship circles.

What the Research Means

Emerging evidence is tracing the pathways of the mind-body interaction. For example, as seen with the college students, chronic feelings of loneliness can help to predict health status -- perhaps because lonely people have more psychological stress or experience it more intensely and that stress in turn tamps down immunity. It's also no surprise that depression hurts immunity; it's also linked to other physical problems such as heart disease. At the same time, depression may both reflect a lack of social support and/or cause someone to withdraw from social ties. Both can be stressful and hurt the body's ability to fight infection.

All of these findings extend what we know about how stress management and interpersonal relationships can benefit day-to-day health, doing everything from helping us combat the common cold to speeding healing after surgery. The research is in synch with anecdotal reports of how people get sick in stressful times, but understanding exactly *how* psychology affects biology helps scientists to recommend the best ways we can build up immunity.

How We Use the Research

Managing stress, especially chronic or long-term stress (even if it's not intense), may help people to fight germs. When burdened with long-term stressors, such as caring for an elderly parent or spouse with dementia, health can benefit from conscientious stress management.

Kiecolt-Glaser and Glaser confirmed this hopeful option by comparing the immune function of exam-stressed medical students given hypnosis and relaxation training with that of students without training. At first, the immune responses of the two groups appeared to both go down. However, closer inspection revealed that some students took this exercise more seriously than others. Those who didn't take relaxation training seriously didn't fare so well; those who practiced conscientiously did actually have significantly better immune function during exams than students who practiced erratically or not at all.

Finally, the newest findings on social stress underscore the value of good friends; even just a few close friends can help someone feel connected and stay strong. Social ties may indirectly strengthen immunity because friends - at least health-minded friends -- can encourage good health behaviors such as eating, sleeping and exercising well. Good friends also help to buffer the stress of negative events.

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Co-Morbidity of PTSD and Immune System Dysfunction: Opportunities for Treatment

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Abstract

Posttraumatic stress disorder (PTSD) is defined as a psychiatric disorder; however, PTSD co-occurs with multiple somatic manifestations. People living with PTSD commonly manifest dysregulations in the systems that regulate the stress response, including the hypothalamic-pituitary-adrenal (HPA) axis, and development of a pro-inflammatory state. Additionally, somatic autoimmune and inflammatory diseases and disorders have a high rate of co-morbidity with PTSD. Recognition and understanding of the compounding effect that these disease states can have on each other, evidenced from poorer treatment outcomes and accelerated disease progression in patients suffering from co-morbid PTSD and/or other autoimmune and inflammatory diseases, has the potential to lead to additional treatment opportunities.

Keywords

Post-traumatic stress disorder; PTSD; Autoimmune disease; Inflammatory diseases; Rheumatoid arthritis

Introduction

Although traditionally considered a type of anxiety disorder, post-traumatic stress disorder (PTSD) is classified as a Trauma and Stress related disorder in DSM-V. PTSD is a chronic psychiatric illness that develops subsequent to experiencing a significant traumatic event. Although exposure to a stressful event is required for PTSD, only a minority (8–18%) [1–3] of trauma exposed individuals go on to develop the disorder. DSM-V criteria for PTSD include delayed onset of behavioral changes that can be grouped into 4 distinct diagnostic clusters: re-experiencing, avoidance, hyper-arousal and negative cognitions and mood.

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PTSD is also a somatic condition, such that patients with PTSD have been found to have biological alterations in several primary pathways involving the neuroendocrine [4] and immune systems [5]. Much like physiological stress, chronic psychological stress stimulates the stress response pathways of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system leading to downstream release of glucocorticoids (GC) and catecholamines. Cortisol, which is the primary endogenous GC hormone in humans, acts on the central nervous system, metabolic system, and immune system to modulate the stress response. GCs impact physiology and behavior by binding to the intracellular GC receptor (GR) on target tissues leading to downstream effects of immunosuppression, increased energy metabolism, and negative feedback inhibition of the HPA axis. In this way, GC signaling is central to the neuroendocrine modulation of the immune system.

PTSD co-occurs with dysregulation of the HPA axis, impaired GC signaling, and the development of a pro-inflammatory state. Not surprisingly, PTSD is associated with poor self-reported physical health as well as high rates of comorbidities, such as cardiovascular, respiratory, gastrointestinal, inflammatory and autoimmune diseases [6–8]. Recently a large retrospective cohort study of 666,269 Iraq war veterans showed a two-fold increase in the risk of autoimmune diseases in individuals with PTSD compared to those without any psychiatric illness and a 51% increased risk when compared to individuals with other psychiatric illnesses [9]. Dysregulations in immune function as a result of the complex interplay between the neuroendocrine and immune systems in PTSD may unmask a predisposition to, or accelerate the progression of, autoimmune (AI)/inflammatory diseases, thereby compounding the disease burden in these patients. In the following sections we will review the mechanistic links between neuroendocrine and immune dysfunctions in PTSD and outline existing and novel pharmacological treatment options that may be able to address both the psychological and biological disturbances observed in patients living with PTSD.

Candidate Mechanisms Linking PTSD and Immune Dysfunction

Reduced Circulating Cortisol

As mentioned above, neuroendocrine alterations in people living with PTSD may precipitate immune disturbances. The dogmatic physiological signature of chronic stress is simultaneous elevations in concentrations of cortisol and catecholamines [5]. Contrary to this dogmatic view, PTSD is associated with low levels of morning cortisol and elevated levels of norepinephrine (NE). Excessive activation of the HPA axis in response to trauma and sustained increases in corticotrophin-releasing factor (CRF) are collectively proposed to downregulate CRF receptors in the pituitary leading to downstream reduction in GC signaling, decreased secretion of cortisol, and subsequently increased GC sensitivity [10]. These changes, along with enhanced sympathetic activity driven stimulation of β2-adrenergic receptor on immune cells, may lead to increased cytokine production, fostering the hyper-inflammatory state frequently co-morbid with PTSD.

An alternative view is that low cortisol concentrations are a precipitator of PTSD rather than a consequence of PTSD. Low salivary and urinary cortisol immediately following trauma have been reported to be predictors of PTSD suggesting that low cortisol concentrations may

in fact be a preexisting vulnerability for developing PTSD rather than a consequence of PTSD [11]. Interestingly, inadequate cortisol secretion in relation to the chronic inflammation observed in rheumatoid arthritis, suggests that the suboptimal production of cortisol may be involved in onset and/or progression of autoimmune disease [12,13]. Hence, overlap may exist between the mechanisms by which low cortisol concentrations may precipitate both psychiatric and somatic diseases and disorders.

However, because of the multifaceted regulation and impact of the GR, information about glucocorticoids alone is not consistently predictive of their function or dysfunction. GRs have extensive variability in their actions depending on the target tissue. Multiple independent promoters present in the GR gene contribute to GR variability by influencing tissue specificity of GR gene expression. Epigenetic modulation of some of these promoters has been demonstrated to change GR gene expression and function in PTSD [14]. Moreover, single nucleotide polymorphisms in the GR gene NR3C1 and the FKBP5 gene (co-chaperone of hsp90 which regulates GR sensitivity) are associated with altered HPA axis sensitivity (GR hypersensitivity or GR resistance) [15]. Hence, alterations in multiple factors including GR expression levels, GR affinity, co-factors, GR heterogeneity and GR density in target tissues are sufficient to affect GC signaling and are candidate mechanisms for enhanced inflammation associated with PTSD.

Chronic Low Grade Inflammation

PTSD is linked to cytokinemia and a recent meta-analysis of 20 studies found increased plasma levels of pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β) & interleukin-6 (IL-6) in individuals with PTSD compared to healthy controls [16]. In addition, there is a prospective association of plasma C-reactive protein (CRP) concentrations with the development of PTSD [17], and higher mitogen induced cytokine production in trauma exposed soldiers correlates with augmentation of PTSD symptoms in response to subsequent stressors [18]. These findings suggest that inflammation may predispose an individual to PTSD, and inflammation may even form the biological basis of stress sensitization [18] that precipitates PTSD after trauma exposure.

The relationship between the HPA axis and cytokines is bidirectional. In addition to the previously discussed effects of the HPA axis on cytokines, cytokines can influence HPA axis signaling and impair cellular processes by stimulating oxidative stress. The sequela that follows cytokine-induced changes in the HPA axis and central nervous system has been proposed to lead to the manifestation of PTSD symptoms [19]. This proposition is consistent with results of a study using the predator exposure animal model of PTSD that demonstrated elevated levels of pro-inflammatory cytokines and reactive oxygen species in the brain (hippocampus, amygdala, pre-frontal cortex) and in the periphery as a consequence of stressor exposure [20]. Conversely, administration of the anti-inflammatory agent minocycline following a laboratory stressor is sufficient to block the development of PTSD-like behaviors in a rodent model [21].

Chronic inflammation is a pathological feature of multiple somatic diseases that are highly co-morbid with PTSD including cardiovascular disease, rheumatoid arthritis, asthma, psoriasis, metabolic syndrome, fibromyalgia, chronic pain syndromes and hypothyroidism.

Common cytokines implicated in enhanced inflammation in PTSD and other diseases may therefore serve as a potent therapeutic target in the treatment of both types of conditions.

Alterations in Innate and Adaptive Immunity

A burgeoning area of study is the relationship between PTSD and innate and adaptive immunity. A recent study of U.S. Marines applied weighted gene co-expression network analysis to RNA-Seq and microarray assessment of peripheral blood leukocyte gene expression taken pre- and post-deployment. The authors reported that PTSD risk and PTSD cases groups both had enhanced differential expression of genes associated with innate immune responses mediated by interferon signaling. These findings add to the authors previous work showing that differential expression of CRP and genes involved in antiviral interferon response were associated with the risk of developing PTSD [22] and suggest that innate immunity up-regulation may be both a risk for, and consequence of, PTSD.

A relationship between PTSD and adaptive immunity is also plausible given that cytokines drive differentiation of T cell subsets, and individuals living with PTSD exhibit elevated cytokine production. To this end, a recent study demonstrated an association between PTSD and a T cell phenotype consistent with increased differentiation of T cells and interpreted as early aging of the immune system [23]. Furthermore, T cells may provide a window into the susceptibility of an individual to psychiatric disorders such that responsiveness of T cells to the synthetic GC dexamethasone prior to military deployment predicted both PTSD and depression following deployment [24]. Collectively, the shifts in T cell biology observed in PTSD push towards a preponderance of CD4+ T helper 1 (Th1) cells over the C4+ T helper 2 (Th2) type cells which correlates with increased plasma levels of Interferon-gamma (IFN-γ) in PTSD [25]. Although mechanisms have not been elucidated to date, Marpe Bam et al., has shown that epigenetic modifications and miRNAs were associated with elevated gene expression of the pro-inflammatory cytokine interleukin-12 (IL-12) in peripheral blood mononuclear cells (PBMCs) of PTSD patients [26]. In addition to PTSD, several autoimmune diseases are associated with alterations of the Th1 versus Th2 cytokine balance including rheumatoid arthritis, multiple sclerosis, type 1 diabetes, and autoimmune thyroid disease. In these somatic conditions, the balance is skewed towards Th1 and an excess of IL-12 and TNF-α production, whereas Th2 and production of anti-inflammatory interleukin-10 (IL-10) appear to be deficient [12].

In addition to shifts in T helper cells, Jergovic et al., found a ~50% decrease in the number of regulatory T cells (T_{reg}) in PTSD patients compared to healthy controls [27]. T_{reg} are essential for controlling immune responses and maintaining self-tolerance by inhibiting auto reactive T cells. A decrease in number and function of peripheral T_{reg} has been associated with the development of multiple autoimmune diseases that are highly co-morbid with PTSD [28].

Telomere Shortening and Premature Immunosenescence

In addition to elevated levels of terminally differentiated T cells and an altered Th1/Th2 balance, PTSD has been associated with the age-related phenomenon of telomere shortening. Chronic inflammation has been shown to accelerate telomere shortening leading

to cellular aging and premature senescence that have been implicated in loss of control of the immune system [29]. Senescent cells are terminally differentiated and no longer fully functional, but instead of undergoing cell death, they exist in a zombie-like state spewing cytokines into the cellular milieu. Telomere shortening has been identified in many autoimmune diseases [30] and is associated with acceleration of the manifestation of age-related diseases. Telomere shortening of leukocytes/PBMCs has emerged as a biomarker of PTSD and a recent literature review of 32 studies between 2001 and 2014 found reduced leukocyte telomere length and increased pro-inflammatory markers in PTSD patients suggesting early immunosenescence [23]. Additionally, PTSD is associated with earlier onset of age-related conditions linked to telomere shortening and increased mortality [31].

Sex Differences and PTSD

Similar to other neuropsychiatric and somatic disorders, sex differences have been reported in the context of PTSD. There are well-known differences in PTSD risk between men and women with women exhibiting a higher frequency of PTSD than men (2:1)[33], not explained solely on the basis of exposure type and/or severity alone. Dias et. al demonstrated that female-specific elevation of pituitary adenylate cyclase-activating peptide (PACAP) and differential methylation of a single nucleotide polymorphism (rs2267735) on the PACAP gene (Adcyap1r1) was associated with a PTSD diagnosis in females, but not in males [32]. Differences in the neuroendocrine response to stress in males and females can be attributed to genomic (as above) or hormonal differences to the neuroendocrine response to stress between the sexes [34].

Additionally, autoimmune diseases disproportionally impact females over males, reflected in the study conducted by O'Donovan et al., showing that women with PTSD were three times more likely to be diagnosed with an autoimmune condition [9]. Interestingly however, the magnitude of PTSD-related increased risk was similar between the sexes and the authors therefore did not find a sex difference in the relative risk of autoimmune diseases in PTSD patients. They did however find that a history of Military Sexual Trauma (MST) and PTSD were associated with the highest risk of autoimmune diseases in both men and women and thus MST was an independent risk factor in the development of autoimmune disease. Notably, the patient populations in a large majority of studies referenced in this paper are composed of combat veterans exposed to the trauma of war. But the finding of MST as an independent risk factor for the development of PTSD points to the possibility that the type of trauma may correlate with severity and/or risk of autoimmune or somatic illness, and warrants further work in this area.

PTSD Treatment Opportunities: Immune System Intervention

The literature summarized here establishes that in addition to the commonly appreciated psychiatric manifestations of PTSD, marked alterations in the neuroendocrine and immune systems exist in individuals living with PTSD. As such, intervention strategies that target neuroendocrine and immune dysfunction may prove beneficial to the treatment of PTSD. A similar angle has been assessed in the context of depression such that a meta-analysis illustrates that elevations in CRP and IL-6 precede development of depression and that

patients with increased inflammation are less likely to respond to conventional anti-depressants and more likely to respond to adjunctive anti-inflammatory treatment [35].

Although mechanistically interventions that target function of the HPA axis and/or GR should prove effective in the treatment of both PTSD and immune dysfunction, these neuroendocrine interventions have had mixed utility which may be due to the pervasive nature of the GR on multiple organ systems. Mifepristone, a GR antagonist, has been reported to effectively improve metrics of PTSD symptoms [36], but a more recent report from the same research group demonstrates improvements in cognition but not in symptoms of PTSD or metrics of physical health [37]. More targeted treatment of GR function, through manipulation of GR co-chaperones such as FKBP5, may be a more advantageous route of intervention given that this type of intervention should leave non-pathological GRs intact [38]. To this end, studies of rapamycin, a drug which, among other things, can alter function of GR co-chaperones, has shown promise in rodent models of PTSD [39] and is already FDA approved and in clinical trials unrelated to PTSD.

Given the potential limitations to interventions at the level of GR and the HPA axis, attention to immune-centric interventions is also warranted. Several pro-inflammatory cytokines elevated in PTSD are also implicated in autoimmune diseases and therefore are uniquely positioned to function as biomarkers for diagnosis and treatment of both conditions. For instance, plasma levels of IL-1β and IL-6 have been shown to positively correlate with PTSD symptom duration and severity respectively [16], and can therefore be used to monitor treatment response in PTSD. Drugs aimed at decreasing concentrations of pro-inflammatory cytokines in the circulation might have dual benefits and help ease disease burden in PTSD patients. Canakinumab, a monoclonal antibody against IL-1β, and anakinra, an IL-1 receptor antagonist, are two such medications that target IL-1β. These drugs have been used in the treatment of rheumatoid arthritis and other inflammatory conditions with positive results [40]. Clazakizumab, a monoclonal antibody against IL-6, is in phase 2 clinical trials to treat rheumatoid arthritis with promising results [41]. Furthermore, in rheumatoid arthritis patients, long term treatment with anti-TNF agents has been shown to raise cortisol levels (inadequate cortisol in relation to inflammation implicated in chronic low-grade inflammation) and normalize the HPA axis leading to rapid clinical improvement [42].

In addition, targeting senescent cells may be an advantageous point of intervention. Senolytics are a new intervention strategy in aging research and in diseases of aging which show particular promise. These treatments target and remove the senescent cells, many of which are believed to contribute to cytokinemia, without damaging healthy cells. This exfoliation of the immune system may confer benefits for both traditional immune disorders and neuropsychiatric disorders with an immune component. Although initial studies used methods for clearance of senescent cells that lacked translational potential, recent work demonstrates successful administration of a pharmacological senolytic agent in a mouse model [43].

In addition to these novel immune-driven interventions, it is important to recognize that some of the existing treatments for PTSD confer immune benefits. SSRIs are first line treatment of PTSD, and have been shown to exert anti-inflammatory effects on T-

lymphocytes, dendritic cells, and neutrophils [44]. Specifically fluoxetine and citalopram were found to exhibit an anti-arthritic effect on murine collagen-induced arthritis and in a human *ex vivo* disease model of rheumatoid arthritis [45]. The anti-inflammatory effect of SSRIs in human rheumatoid arthritis tissue was due to reduction of spontaneous cytokine production from macrophages (IL-6, INF-γ and IL-10) through toll-like receptors. Previous studies have found SSRIs to improve symptoms in encephalomyelitis, a multiple sclerosis model through reduction in pro-inflammatory cytokines [46–48]. Other drugs used in the treatment of PTSD that have been found to have anti-inflammatory effects include prazosin (alpha-1-adrenoreceptor blocker) and ketamine. Prazosin has been shown to be effective in treatment resistant cases of PTSD in which recurrent nightmares are problematic [49]. Previous studies have found prazosin and doxazosin, also an alpha-1 blocker, to exhibit anti-inflammatory effects in rodent models of inflammation by inhibiting the production of lipopolysaccharide induced pro-inflammatory cytokines TNF-α and IL-1β [50,51]. Ketamine infusion has been shown to have a rapid reduction in symptom severity in patients with chronic PTSD [52] and ketamine possesses anti-inflammatory actions which have been attributed to inhibition of transcription factors activator protein-1 and nuclear factor (NF)-κB, as well as lowering of serum levels of IL-6, TNF-α, inducible nitric oxide synthase and CRP [53].

Conclusions

Although once believed to be an immune-privileged site, the bidirectional communication between the brain and periphery is now commonly appreciated. The growing recognition that neuropsychiatric disorders are also somatic disorders will improve understanding of disease pathogenesis and lead to advances in treatment options. In the case of PTSD, the relationship with the immune system appears to be multi-tiered and bidirectional. Continued monitoring of developments in immunological interventions and efforts to apply these interventions to PTSD is essential to advancing biological psychiatry. Furthermore, given the bidirectional nature of the relationship between PTSD and immune system function, recognition and treatment of PTSD may improve immunological outcomes for individuals living with primary disorders of the immune system.

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Highlights

- PTSD co-occurs with somatic diseases.
- PTSD is commonly associated with neuroendocrine and immune dysfunction
- Targeting neuroendocrine and immune dysfunction may improve PTSD symptoms.
- Targeting PTSD may improve somatic co-morbidities.
- Translational reciprocity between biological psychiatry and immunology may advance treatment options.

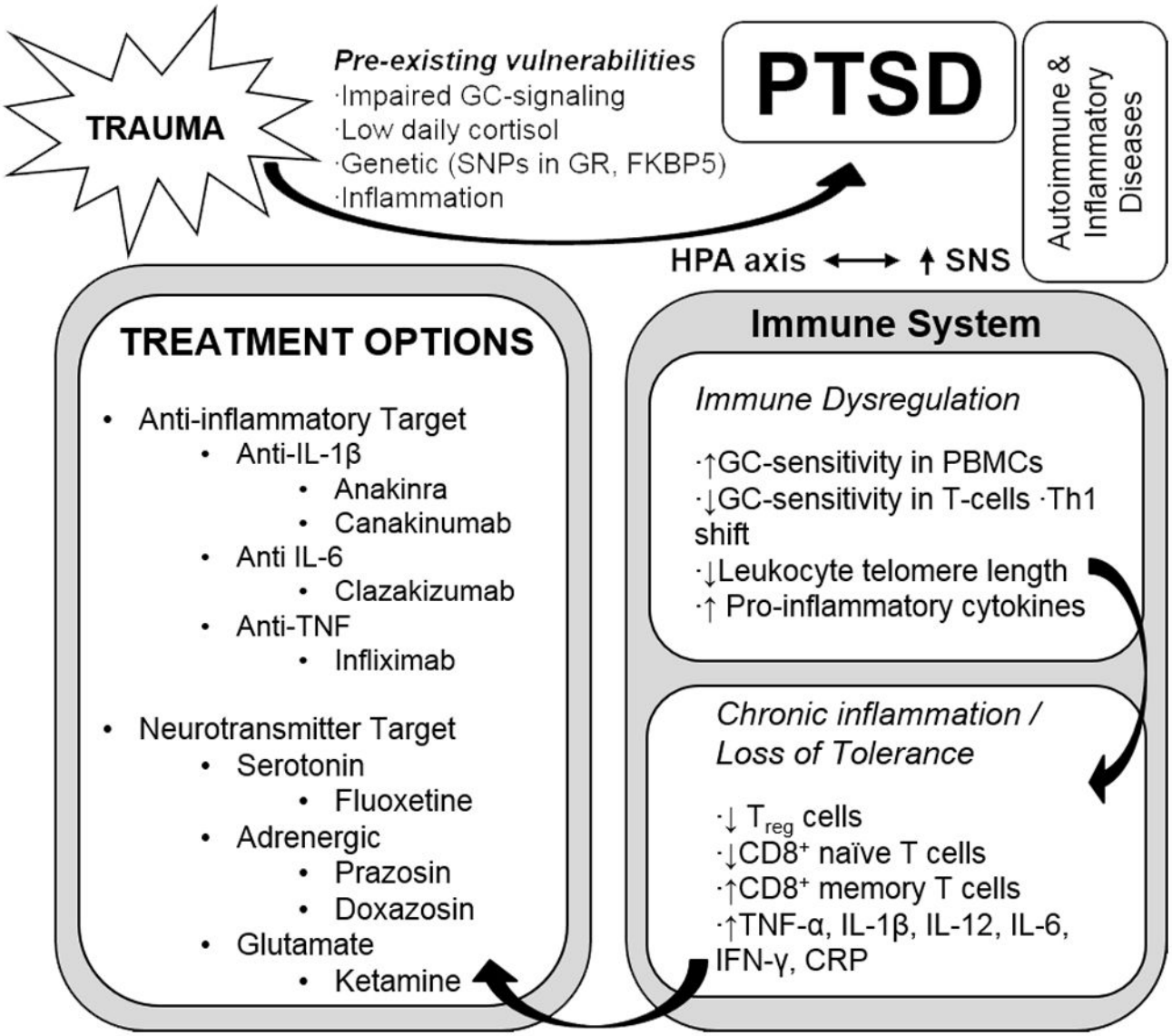

Figure 1. A Psychoneuroimmunological Model of PTSD

Exposure to severe psychological trauma in the presence of pre-existing risk factors leads to PTSD. Immune system changes in PTSD include altered glucocorticoid (GC) sensitivity in target immune cells, shifts in immune cell distribution, immunosenescence, elevated pro-inflammatory cytokines and a decrease in regulatory T cells. A complex interplay of the biological alterations in the stress response known to exist in PTSD, along with immune alterations, are hypothesized to increase the risk for co-morbid somatic autoimmune and inflammatory disorders. Immune interventions may improve both primary PTSD symptoms and co-morbid somatic disorders related to the immune system.