

CERTAIN ASPECTS OF IMMUNOPSYCHIATRY

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SUMMARY

Immunopsychiatry is based on the assumption that schizophrenia, bipolar disorders, and major depressive disorders are related with atypical immune reactions or inflammatory processes. It has also been suggested that the neurotoxic effects of COVID-19 due to the perverted autoimmune reaction could offer fresh acumens into psychotic process. Even acute psychotic symptoms have a subtle pre-psychotic phase and unless treatments are aimed at this preceding phase, newer therapies are not going to achieve their targets. Identifying biosignatures of psychotic disorders lead to better understanding of the etiological mechanism involved in such disorders and aid early diagnostic assays. Interestingly, the search for biomarkers also stimulates new experimental treatment strategies as evidenced by the experiments of newer immunological therapies for psychotic disorders. Characterizing biosignatures are thought to play a significant role in the early detection, treatment, and implementation of preventive strategies in psychotic disorders. The search for identifying biosignatures should go hand in hand with newer experimental therapies for psychotic disorders for the benefit of introducing treatments at an early stage of psychosis development. The identification of biomarkers may lead to a shift from symptom based diagnostic category into subtypes based on immunological alterations and brain biology and such a change might have an advantage to make more precise diagnosis aiding better treatment. The field of immunopsychiatry requires more research to put their findings in context.

Key words: biomarkers – autoimmunity – biosignatures – psychosis - phenotypes

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INTRODUCTION

The classification, diagnosis, clinical management and understanding of the underlying pathogenic mechanisms of psychotic disorders still remain a moot point as there is an overlapping of aetiology and symptomatology. When Emil Kraepelin planted schizophrenia (SCZ) and bipolar disorder (BD) in the garden of psychiatry, he found that their roots entwined. The novel viral infection rekindles a fresh interest in the viral and autoimmune aetiology of a subset of SCZ and other psychotic disorders. Certain mechanisms underlying anxiety and mood disorders as well as psychosis can be shaped by innate and adaptive immune systems interactions (Najjar et al. 2013). As an emerging specialty, immunopsychiatry may require the combined knowledge of immunology and psychiatry. This new specialty is yet to offer any form of relief to the unparalleled human sufferings that psychotic disorders have caused. Physicians and researchers are even winning the race to find treatments and vaccines against new variants of COVID-19 and improving the already available ones. On the other side of the coin, psychotic disorders have been with us from time immemorial and yet they remain a mystery; the researchers might have been barking at the wrong trees.

The neurotoxic effects of COVID-19 are an eye-opener to the impact of an autoimmune reaction on the nervous system and understanding the autoimmune etiology of psychotic disorders (Butler et al. 2020, Pandarakalam 2020). The literature on the autoimmune

etiology of SCZ, bipolar disorder and other psychotic disorders are flourishing (Mayorova et al. 2021, Davison 2012, Pandarakalam 2013, 2015, Rege & Hodgkinson 2013). The autoimmune views explain only the etiology of psychotic disorders and not the dynamics of their symptomatology which also involve disorders of consciousness (Pandarakalam 2019). Psychosis is a common presenting feature in antibody-mediated encephalitis which is treatment responsive. Such an observation has stimulated an interest in estimating the prevalence of antibodies against antibodies - especially antibodies against the N-methyl-D-aspartate receptor (NMDAR). Immunity based therapies are in the horizon but identifying biomarkers of psychotic disorders are a priority for the successful implementation of such ambitious therapies. We can also gain new wisdom from the already existing psychotropics if we pay attention to their immunoregulatory properties along with their neuromodulation. All the above findings offer new insights into the evolving landscape of immunopsychiatry.

IMMUNE DYSREGULATION IN PSYCHOSIS

It is puzzling how immunological surveillance of the CNS is possible without lymphatic supply. Thus, to a great extent, brain-immune interactions are unclear. However, a functional lymphatic vascular network has been found by two recent independent studies lining the dural sinuses of dissected mouse brain meninges

(Louveau et al. 2015, Aspelund et al. 2015). Venous blood from the brain is collected by the internal and external cerebral veins which drain into the dural sinuses. Ultimately, the dural sinuses connect to the internal jugular veins. The structures that were observed exhibited lymphatic endothelial cell molecular characteristics, transported both immune and fluid cells from the cerebrospinal fluid (CSF), and were connected to the deep cervical lymph nodes (Louveau et al. 2015, Aspelund et al. 2015) Stagnation of autopsy specimens of human dura in one of the studies suggested the presence of a probable lymphatic structure similar to the one discovered earlier on, however, the evaluation and characterization of meningeal lymphatics in the human CNS require further studies. The above-mentioned discovery calls for a review of the basic notions in neuroimmunology. If it is confirmed that these vessels exist in humans, it may follow that dysfunction of meningeal lymphatic vessels plays a role in CNS autoimmune diseases such as SCZ, multiple sclerosis, Alzheimer disease, and mood disorders (Miller 2016).

The contributory role of NMDAR hypofunction in SCZ has been suggested by multiple converging lines of research evidence (Coyle 2012). The full spectrum of symptoms seen in schizophrenia are produced from pharmacological blockade of NMDAR, also, neuropathological findings of reduced numbers of inhibitory GABAergic interneurons and reduced dendritic spine density that are compatible with a model of NMDAR blockade have been reported (Coyle 2012, Zhang et al. 2008). In particular, both the common and rare variants of the susceptibility genes for SCZ are associated with the adaptive immune system and glutamatergic transmission (Harrison 2015).

In a study to assess the presence of NMDAR among 228 - first-episode psychosis patients, Lennox et al concluded that some patients with first-episode psychosis had anti-NMDAR antibodies that might be relevant to their illness but were not different from patients without NMDAR antibodies in clinical characteristics urging more studies of antibodies in the context of psychosis (Lennox et al. 2017). The authors argue that the presentation of schizophrenia-like psychosis only in a very few cases would have serious outcomes both for treatment and nosology, for the reason that affected patients might respond to immunotherapy as a substitute for antipsychotics or psychological interventions. Normally, no mere increase of dopamine is observed in the neuronal system in presence of dopamine overactivity, indicating a weakness in the dopamine hyperactivity hypothesis of SCZ. The dopamine overactivity in the absence of dopamine excess warrants some other biomechanism responsible for this biological activity.

The likelihood that brain-reactive antibodies are solely responsible for some cases of psychosis has generated substantial enthusiasm. This is because N-

methyl-D aspartate receptor and voltage-gated potassium channel-complex antibodies have been reported in a few first-episode psychosis patients (Gaughran et al. 2018). Immunopsychiatry search for the precise processes by which specific neuroimmune effects are completed. Cytokine storm, the autoimmune reaction occurring at the height of COVID-19 infection in some individuals, is responsible for the COVID-19 complications and the viral precipitation of an autoimmune disorder, is a well-recognized phenomenon. Surprisingly, autoimmune etiology has been suggested for obsessive-compulsive disorders (Maina et al. 2009, Gerentes et al. 2019, Pearlman et al. 2014). In a subset of OCD patients, it has been hypothesized that anti-brain antibodies cross-react with basal ganglia tissue. Anti-autoimmune antibodies for treatment of pemphigus have been suggested (Payne et al. 2009).

The many processes involved in autoimmune reactions are unclear and attempting to identify the exact aetiology of autoimmune related conditions in the autoimmune sphere may look like finding a needle in the haystack (Pandarakalam 2021). Metaphorically, SCZ is like a tsunami, the cause of tsunami is not in the seawater, but underneath the seabed, the shifting of tectonic plates. Similarly, the etiology of the symptoms of SCZ may be in the immune system, but the actual psychotic symptoms (the tsunami) involve disorders of consciousness mediated through the brain (Pandarakalam 2019). The existing neuromodulating antipsychotics serve only the function of the "floodgates" to stop the tsunami. Autoimmune views of psychosis strengthen the concept of immunopsychiatry.

The view that psychosis could be an autoimmune disorder is also hopeful for the sufferers and those predisposed to it, in the sense that giving more attention to physical aspects of health could have a preventive effect along with maintaining psychological health. External factors such as exposure to UV radiation, obesity and cigarette smoking, have all been implicated in worsening of autoimmune disorders, potentially due to increased oxidative stress and systemic inflammation. One wonders whether such principles are also applicable in the case of psychotic disorders; clinicians have so far been paying attention only to psychological factors. In a recent study, it has been found that a combination of healthy lifestyle behaviours acts synergistically to mitigate the biological processes involved in the development of systemic lupus erythematosus signifying that healthy lifestyle measures should be adopted to help reduce the risk of developing autoimmune disorders like SLE (Choi et al. 2021). It could be suggested that maintaining a healthy lifestyle such as regular exercise, weight watching, non-smoking, moderating alcohol intake, good sleeping habits, balancing immune system and maintaining similar healthy lifestyle behaviors could have a positive effect in reducing the risk of SCZ and BD even when there is high genetic burden.

BIOSIGNATURES

Bio-signatures of psychotic disorders could be explored with immunopsychiatry. Consequently, the risk, state, trait, and prognosis of various psychiatric disorders might be indicated. If the autoimmune aetiology of psychotic disorders is true, we are currently treating only the complications of the disorder with antipsychotics and we are in a comparable position to that of the pre-insulin era in the treatment of diabetes mellitus. Moreover, the antipsychotics that are essentially aimed at regulating the dopamine excess might be indirectly precipitating more accumulation of the autoimmune factors in the pre-neuronal sites that fundamentally account for the dopamine overactivity leading to psychotic symptoms. So, it is vital to detect and address the autoimmune dynamics to control the psychotic process; biosignatures are extremely important for the early detection and treatments.

The viral precipitation of autoimmune disorder is a well-founded phenomenon. The psychiatric diagnoses are not based on the use of laboratory tests, exam findings, or other scientific tools in the identification of discrete mental disorders. What is diagnosed as mental disorder is overly sensitive to professional and social contextual forces and mental disorder has such fluid boundaries with normality. Valuable information about brain functioning has been provided by electroencephalography and magnetoencephalography in psychosis. The lack of definitive biological parameters is the major drawback in the use of psychiatry to predict and prevent psychosis.

Neurophysiological alterations have been reported to exist hitherto the prodromal period before psychosis development and they make promising tools for predicting a future transition to psychosis. The detection of such biomarkers has become a major research. Basically, psychiatrists are physicians who are used to physical parameters in clinical diagnosis. In order to effectively predict the onset of psychosis, clinical approaches with objective biological parameters are required.

Immunopsychiatrists search biomarkers beyond the neurological dimensions of psychotic disorders. They argue that baseline systemic immune-inflammation index (SII) resonates the immune response and systemic inflammation based on peripheral lymphocyte, neutrophil, and platelet counts, and they are associated with scores of depressions and anxiety. The balance between host systemic inflammation and immune response status can be marked objectively by SII. The production of local and systemic cytokines, chemokines, and other inflammatory mediators demonstrates how the immune system responds to coronaviruses (Cameron et al. 2008). It has been suggested that T-helper-1 cell functions are activated in SARS and MERS patients due to the presence of high levels of Interleukin (IL)-1 β , IL-6, Interferon (IFN)- γ , CXCL10, and CCL2 in these patients. Moreover, elevated levels

of T-helper-2 cell-secreted cytokines (such as IL-4 and IL-10) were uncovered in Covid-19 patients, unlike in SARS and MERS (Ye et al. 2020, Channappanavar & Perlman 2017).

Cytokines' dysregulation (especially IL-1 β , IL-6, IL-10, IFN- γ , TNF- α , and transforming growth factor- β (TGF- β)) are known to involve factors linked with psychiatric disorders (Poletti et al. 2019, Benedetti et al. 2020). It is recognised that biological interaction pathways between immune systems and psychopathological mechanism behind psychiatric disorders include neuroinflammation, blood-brain-barrier disruption, peripheral immune cell invasion into the central nervous system, neurotransmission impairment, hypothalamic-pituitary adrenal axis dysfunction, microglia activation and indoleamine 2, 3-dioxygenase induction (Dantzer 2018). It is now ever more documented that infection can trigger perturbation of the immune system that could induce psychopathology, and psychiatric sequelae were observed after previous coronavirus outbreaks (Mazza et al. 2020). Biomarkers of psychiatric disorders that are already in their prodromal phase can be identified via the insights mentioned above.

The search for biomarkers has not been limited to immunology. Advances in genetics have led to the identification of associations between genes involved in the regulation of the immune system and an increased risk of SCZ which is polygenic and leaves observable phenotypes due to the interaction of genotypes with the environment. These phenotypes have low predictive power for identifying individuals who will become psychotic, but they do serve as biomarkers for pathophysiological processes that can become the targets of prevention tactics (Freedman et al. 2005). Genetic studies may serve as another route to search for biosignatures. Current genetic research has begun to identify genes associated with SCZ, some of which have phenotypes that appear early in life. The discovery of BD endophenotypes can improve early diagnosis, prevent errors in treatment and help elucidate the genetic vulnerability for this serious disease (Luchezar et al. 2013).

Gene overlapping with different forms of psychotic disorders pose serious problem in identifying and relying on potential susceptibility genes in psychotic disorders. So, the study of susceptibility genes alone may not be sufficient to arrive at correct diagnosis. Better understanding of the interplay between multiple environmental, immunological, and genetic factors involved in the pathogenesis of psychosis could provide relevant information for the differential diagnosis and treatment of such disorders. Future studies on the role of these factors in psychotic conditions may greatly benefit by using a combined approach with multiple research tools incorporated into a single study.

The gold standard of traditional classification of psychosis is based on observable clinical symptoms which are like fever and infection that may have multiple causes. Identification of biomarkers could

eventually lead to more precise diagnosis and so helpful in finding effective novel treatment strategies. It might also open up opportunities for repurposing the existing drugs that are being used for other medical conditions. In the event of confusing clinical presentation, clinicians could also take advantage of immunobiologically distinctive diagnosis in the years to come. Deviating from diagnosis based on clinical phenomenology, Clementz et al. have proposed three neurobiologically distinct biotypes highlighting a possible advantage of neurobiological versus clinical categorization schemes for differentiating psychotic disorders (Clementz et al. 2016).

ETHICAL ASPECTS

Psychotic symptoms could occur in normal people, it is the frequency and duration of these symptoms that make them abnormal. A good comparison is that breathlessness and palpitations that may occur while doing exercises without making them symptoms of physical disorders. While searching for biomarkers, we are also approaching the quick sands of medical ethics and finding biomarkers of psychotic disorders may brush with medical ethics. After evaluating the literature on biomarkers, Hinimaa M and Larsen TK cautions that conceptualization of early psychosis is often inconsistent and even misleading and ethical discussions mostly concern 'false positives' risk assignments, stigmatization, informed consent, and appropriateness of treatment procedures (Heinimaa & Larsen 2002). Incorrect positives could term out to be a life sentence for some individuals. Medico-legal aspects of biomarkers which can be used and abused in a court of law need special consideration. With the introduction of the potential biomarkers, the distinction between mental abnormality/ strangeness and mental disorder could become clearer. Lawyers underestimate the former and mental health professionals tend to overestimate or even medicalise them.

While searching for biomarkers and innovative new therapies, immunopsychiatry runs the risk of deteriorating as mindless psychiatry and ultra-reductionism if newer developments in consciousness studies are ignored. The current research views in consciousness studies point towards potential independent existence of consciousness and possible survival after physical extinction (Moody 1988, Stevenson 1997, Schwartz 2002, Fontana 2009, Fenwick 2012, Tynn 2021). It is high time that such non-reductionist views are considered in the mainstream of psychiatry. At this juncture, it is useful to recognize the works of Kelly et al. who has argued convincingly in favour of the irreducibility of mind (Kelly et al. 2007). Without adequate knowledge of anatomy, surgeons could be like pre-scientific surgeons and likewise, psychiatrists without an expanded model of brain-mind-consciousness complex could be stuck in the prescientific era.

THERAPIES IN TRIAL

Currently, different forms of experimental therapies have been speculated to be potentially useful in the treatment of psychotic disorders. Immunosuppressant therapy involves taking an immunosuppressant, which targets a specific part of the immune system responsible for homeostatic immune imbalance. The immunosuppressant used in this therapy is called rituximab. Its mode of action is to kill the cells which produce the pathogenic antibodies linked to antibody-associated psychosis. Moreover, it is assumed that when these cells are destroyed, the body cannot generate the pathogenic antibodies, thereby reducing the symptoms of psychosis.

There has been a keen interest in identifying novel molecular therapeutic targets, owing to the achievements of therapeutic immunoglobulins that are presently available. Initially, immunodeficiencies were treated with Intravenous immunoglobulin G (IVIG), however, it is currently used as replacement therapy in primary and acquired humoral immunodeficiency and as an immunomodulatory therapy in autoimmune disease and transplantation. Self-reactive immunoglobulin gamma antibodies contribute to the pathology of autoimmune diseases and paradoxically, they are used to treat inflammatory diseases in the form of high dose IVIG (Pagan et al. 2018). Primarily, IVIG therapy is the treatment option for situations where there is an immune deficiency, or the immune system is overactive. Subcutaneous immunoglobulin G (SCIG) is used to refer to the administration of IgG antibodies subcutaneously. Immune deficiencies that lead to low levels of IgG may be primary or secondary to another disorder, injury, or event.

IVIG can be used in the treatment of several primary immune deficiencies including common variable immune deficiency (CVID), IgG subclass deficiency, and X-linked agammaglobulinemia. IVIG may also be administered due to low IgG secondary to conditions like bone marrow transplantation, Myeloma, and chronic lymphocytic leukaemia. When used to treat autoimmune or inflammatory disorders, IVIG is usually administered at higher doses. Vasculitis, Guillain-Barre syndrome, and myasthenia gravis are examples of autoimmune and inflammatory conditions where IVIG therapy is commonly applied to control the overactive immune system.

IVIG therapy involves giving healthy antibodies to patients collected from people's donated blood. The beneficial, healthy antibodies are administered directly into the blood. By sticking to the antibody-producing cells, the healthy antibodies try to prevent them from producing more of the pathogenic antibodies linked to antibody-associated psychosis. though, with contributions that are yet unknown for various diseases, several potential mechanisms for the effects of IVIG have now been identified (Looney et al. 2006). Fc-dependent and/or F(ab')₂-dependent non-exclusive mechanisms of action have been speculated to be concerned with

the mode of action of IVIG. There is a broad interaction between IVIG the different components of the immune system, and apart from maintaining immune homeostasis, IVIG also impacts effector functions of immune cells (Graff-Dubois et al. 2007).

Monoclonal antibodies share the same target object and are produced in identical cells, usually via unnatural means. They have a wide range of applications including medical uses. Up till now, only two cytokine-based immunotherapy studies in SCZ have been published, although several other trials are ongoing. The first is a case series of 2 patients treated with interferon gamma-1b for treatment-resistant SCZ and had - significant improvement in total psychopathology (Gruber et al. 2014). The second, an 8-week open-label trial of adjunctive tocilizumab (an anti-interleukin-6 receptor monoclonal antibody) in 6 patients with schizophrenia, which was associated with significant improvements in cognition, was recently published by our group (Miller et al. 2015). mechanisms of action of monoclonal antibodies, like IVIG, include target cell cytotoxicity via cytotoxicity mediated by complement or antibody-dependent cells, induction of apoptosis of target cells, blockade of co-stimulatory molecules, and neutralization of pathogenic antibodies and soluble factors such as cytokines and their receptors and these activities eventually lead to rectification of the inflammatory process (Bayry et al. 2007).

Successful trials of neuroactive steroid like Zuranolone points towards the immunological dysregulation that may accompany in major postpartum depression which sometimes progress into BD. Therapeutic effects of a drug indirectly give clues to the aetiology of the disorder in medicine even though such therapeutic diagnosis have no entry into the official diagnostic classifications. Zuranolone is an investigational neuroactive steroid currently being researched for postpartum depression in phase iii. Zuranolone is a positive allosteric modulator of GABAA receptors, the same type of drug as brexanolone, which FDA approved in March 2019. Zuranolone comes in a capsule form and brexanolone is administered in a continuous infusion over a total period of 60 hours. The results of one of them, an outpatient trial in women with postpartum depression were published recently published (Deligiannidis et al. 2021). The main advantages are the rapid response on Day 3 of treatment and the sustained response after treatment cessation on Day 15. This neuroactive steroid drug was generally well tolerated bearing in mind that steroids can exacerbate symptoms of SCZ.

A few of these treatments have been used and approved for other health conditions, but they are not currently licensed to treat antibody-associated psychosis warranting more research evidence. However, they can be given under “off-label prescribing” as add-on therapy. These therapies involve their own side effects, and steps to minimize the side effects should be undertaken.

IMMUNOMODULATION OF PSYCHOTROPICS

Certain psychotropic drugs with immunomodulatory effect work more efficiently than others and such a property itself points towards the immunological link of psychotic disorders. Such fresh insights can enrich the evolving field of immunopsychiatry. Undoubtedly clozapine has been a transformative drug for SCZ, but its superior effect is mainly attributed to neuromodulation. One reason for such an omission is the neurological based etiopathogenesis of SCZ ignoring the autoimmune aspects. There are suggestions that clozapine (CZP) and haloperidol may work more on immunomodulation than on neuromodulation (Leykina et al. 1997). CZP is undoubtedly a far superior drug in comparison with other antipsychotics. The superiority of CZP over other antipsychotics could be due to its probable partial immunosuppressant/immunomodulatory effects and inhibition of dopaminergic transmission.

The immunomodulatory property of CZP supports the autoimmune etiological hypothesis of SCZ, thereby stabilizing the very foundation of immunopsychiatry. If the autoimmune etiology of an SCZ subgroup is validated, then several existing drugs could be repurposed and prescribed based on their actions on the immune system (Baumeister et al. 2016). Other immunological abnormalities associated with CLZ include elevated serum immunoglobulin levels (DeLisi et al. 1985), decreased mitogenic response of peripheral blood lymphocytes to phytohemagglutinin and pokeweed mitogen (DeLisi et al. 1985, Ganguli et al. 1987), the presence of morphologically abnormal large lymphocytes in the blood and bone marrow, increased serum IL-2 receptor levels (Chengappa et al. 1995), decreased IL-2 levels (Wilke et al. 1996), IFN-g production (Ganguli et al. 1989), and a high serum level of IL-6 (Shintani et al. 1991).

An increase in T suppressor lymphocytes in drug-naive SCZ sufferers and T helper lymphocytes in drug-treated patients was noted by Masserini et al. (1990). If subgroups of patients are validated to be characterized by factors such as infections, autoimmunity, inflammation, and immunogenetic-mediated response to environmental factors, then several existing drugs could be repurposed and prescribed based on their actions on the immune system (Baumeister et al. 2016). Such conjectures strengthen the foundation of immunopsychiatry.

Plaza et al. observe that psychiatric patients in a Paris mental health center were spared from COVID-19 even though many cares in the same unit caught the virus (Plaza et al. 2020). They attribute this result to the immunotherapeutic effects of psychotropic drugs. CZP users were thought to be more vulnerable to COVID-19, but curiously, patients not on higher doses were not observed to have greater infection rate. If the autoimmune etiology of SCZ is accepted, then it can be hypothesized that specific “anti-auto antibodies” may be the way toward halting the autoimmune reaction respon-

sible for the SCZ process (Pandarakalam 2019). Such ideas are being considered in the treatment of autoimmune disorders (Jose et al. 2017, Payne et al. 2008). Among other psychotropics, lithium has also immunoregulatory effect and antiviral effect against Herpes simplex, Epstein-Barr and Borna viruses (Marneros & Angst 2000, Rybakowski 1999). Chlorpromazine is also thought to have immunoregulatory effect and possibly antiviral effect (Plaze et al. 2020, Stip et al. 2020). Even though CLZ users were thought to be more susceptible to COVID-19, there are no reports of higher incidence among them and the cause of this anomaly entails further clarification.

Psychotropic drugs may either inhibit the viral replication or block the cytokine storm, or both. A potential mechanism of action of psychotropic drugs is modifying the balance between pro and anti-inflammatory cytokines, which could protect against the most deleterious consequences of an indiscriminate immunological response (Baumeister et al. 2016). Patients hospitalized for severe COVID-19 have been found to be benefiting from the use of functional inhibitors of acid sphingomyelinase, including antidepressants and antipsychotics (Hoetrel et al. 2021).

CONCLUSION

The autoimmunological etiologic hypothesis of a subset of psychotic disorders is getting well established. Because of the complex and multifactorial nature of SCZ, BD and other psychotic disorders, it would be difficult to identify a single, sensitive, and specific biomarker in individuals predisposed to psychosis. For immunity-based treatment strategies to be successful, early detection of psychotic disorders is vital so as to nip in the bud before neurological damages have occurred. So, research to identify new treatment strategies should go hand in hand with the detection of biomarkers. The recognition of biomarkers would help to divert the already existing drugs in pharmacology for psychotic disorders. The classification criteria in psychiatry will have to be rewritten in the years to come.

Immunity-based experimental therapies are in their early stages, but we have reasons to be optimistic about them. So far, no definite biomarkers have been identified. The superiority of clozapine over other antipsychotics may be due to its immunomodulatory properties along with neuromodulation and such a conjecture support the search for immunity-based newer therapies. The study of antibody mediated psychosis has the potential to deliver an exclusively brand-new treatment option for a small proportion of individuals with psychosis and these are early days to comment on the success of such treatments.

Without being an opportunistic scientist or incognizant of the pain COVID-19 is inflicting on the suffers and their dear ones, it could be suggested that studies of this novel virus might help new research pathways in diagnostic technologies and treatment strategies of

psychiatric conditions. Effective vaccinations against COVID-19 were identified in such a short time span, so we have reasons to be optimistic about identifying newer treatment techniques for psychotic disorders that were daunting to all humanity possibly right from the beginning of the human race. A few centuries ago, a part of asylums was occupied by patients with pellagra psychosis, and that situation has completely changed when the causative factor was identified as deficiency of niacin. Let us hope that such a scenario would hopefully happen in the future when these new etiological research progress and with the introduction of newer treatment strategies. If that is an unachievable target, psychotic conditions would hopefully become manageable like Diabetes Mellitus. Scientists from around the world are joining together in a bid to stomp out the devastating pandemic and expectantly, such a spirit of unity would continue in the post-pandemic period to find cure for several other diseases including psychotic disorders.

Immunopsychiatry is running the risk of growing as mindless psychiatry and the only way out of such an unwelcome development may be that the followers of this fledgling speciality should also focus on the recent growth of consciousness studies. Immunopsychiatry urges cognitive scientists to search for greater mind and consciousness. Immunity dysregulation may be the underlying mechanism of a subset of psychotic disorders, but the precipitating and perpetuating factors may be psychosocial disturbances. Ignoring the different dimensions of human existence may be equivalent to downgrading homo sapiens to the level of electrical animals. Immunopsychiatry, though highly promising from a clinical perspective, might reinforce the already existing reductionist psychiatry and the solution to solve this riddle is promoting more research into deeper aspects of consciousness and mysticism. These are tempestuous and adventurous times in psychiatry. Investigators are searching for 'new continents' and those who are trying to discover new oceans should be prepared to lose sight of the shores.

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