Schizophrenia Research
A Progress Report

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KEYWORDS

• Schizophrenia • Research discoveries • Treatment approaches
• Autoimmune diseases • Regenerative medicine • Head trauma • Early intervention
• Antipsychotics

KEY POINTS

- The collection and use of large collaborative databases has facilitated more detailed genetic inspections in schizophrenia.
- Recent studies highlight the immune hypothesis of schizophrenia, building on prior epidemiologic and postmortem research.
- Regenerative medicine is now coming into schizophrenia research.
- Emotional trauma in childhood is associated with a higher rate of schizophrenia in adulthood.
- One conspicuous change in recent years has been the refocusing of the field on the earliest stages of schizophrenia in the hopes of early intervention or even primary prevention in an effort to reduce long-term morbidity.

In keeping with the year-end synopsis focus of this special issue of *Psychiatric Clinics of North America*, this brief review focusses on key research discoveries and recent reports. Some discoveries advance our understanding of schizophrenia's causation and others advance treatment approaches. Collectively, this synthesis should also convey to the discerning reader an overall sense of the state of play of translational research and clinical practice for schizophrenia.

Although the neurobiology of mental illnesses in general—and in this instance schizophrenia—remains elusive, several recent studies point to some convergence in the genetics of schizophrenia. The collection and use of large collaborative databases have facilitated more detailed genetic inspections in schizophrenia. Two studies are illustrative. The Psychiatric Genomics Consortium conducted a large genomewide association study that found substantial overlap in risk loci between schizophrenia,

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mood disorders, autism, and attention deficit disorders.[1] In another large study involving 37,000 patients and 114,000 normal subjects, the Schizophrenia Working Group of the Psychiatric Genomics Consortium[2] found 108 gene loci that were associated with schizophrenia.[3] The loci implicated were in genes that involve dopamine synthesis, calcium channel regulation, and glutamate neuroreceptors. Additionally, there was substantial overlap with immunomodulatory genes, thus, adding to the growing literature on immune dysfunction in schizophrenia.

Other recent studies also highlight the immune hypothesis of schizophrenia, building on prior epidemiologic and postmortem research. Benrós and colleagues[4] examined a Danish registry of autoimmune diseases involving some 142,000 patients with known autoimmune diseases and some 39,000 patients with schizophrenia. They found strong relationships, including that 3.1% of patients with autoimmune diseases also had a positive family history of schizophrenia. Moreover, autoimmune diseases were observed in 3.6% of patients with schizophrenia. Another Danish registry study by Wium-Andersen and colleagues[5] found a substantial increase in C-reactive protein—a nonspecific marker of inflammation—in patients with schizophrenia. This immune hypothesis has gained traction in our field. In another broad overview, Steiner and colleagues[6] also highlight the overlap between immune dysfunction, schizophrenia, and glucose regulation. Kirkpatrick and Miller[7] provide a synthesis of findings to date, making the point of mind-body dualism in immune dysfunction in schizophrenia.

Although perhaps some skeptics might view recent immune findings as "old wine in a new bottle," it is different and encouraging to see that entirely new area of research—namely regenerative medicine—is now coming into schizophrenia research. This new area has considerable potential. To that end, Wright and colleagues[8] provide an exciting, yet scientifically terse, overview of emergent stem cell research in schizophrenia. Another, albeit small, study[9] of cultured fibroblasts from patients with first-episode schizophrenia replicated an earlier finding of elevation of plasma caspase-3 neurodegenerative enzyme in schizophrenia.[10]

Other known risk factors for schizophrenia have been studied recently. Orlovska and colleagues[11] found a 1.64-fold higher risk of schizophrenia in people who had suffered a head injury. Molloy and colleagues[12] also reported a similar effect in another large epidemiologic study. In addition, these authors[13] also found that emotional trauma in childhood is associated with a higher rate of schizophrenia in adulthood. This finding replicates earlier British work in this area and suggests that there is an inherent vulnerability to brain insults—infectious, traumatic, and psychological—that can predispose to later schizophrenia.

One conspicuous change in recent years has been the refocusing of our field on the earliest stages of schizophrenia in the hopes of early intervention or even primary prevention.[14] Although the field of prodromal research is burgeoning, it is still sobering (at least from a treatment perspective) that the conversion rates to psychosis remain too low—and too difficult to predict for any given patient—to espouse the use of antipsychotic medications in people who exhibit (merely) prodromal symptoms. To that point, Fusar-Poli and Yung[15] summarized the psychosis conversion rates over time among prodromal populations as follows: 18% conversion at 6 months, 21% at 1 year, 29% at 2 years, and 32% at 3 years. It seems that the conversion rate levels out after 3 years at an overall rate of 36%. This point is underscored by the 10-year conversion rate of almost 35% in the longitudinal PACE 400 Australian study.[16] It is debated that early cognitive decline might be a clinically detectable and core feature,[17,18] although this still seems too nonspecific to be of early diagnostic value.