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Guest Editorial

How Does Untreated Psychosis Lead to Neurological Damage?

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The idea that early treatment leads to better outcomes is a standard in medicine. From cancer to coronaries, we find that detection early in the disease course offers better prognosis. The longer a pathological process is left unchecked, the more damage is done; illnesses become more complex, thus they become more difficult to treat.

In chronic diseases, such as diabetes, which have multifactorial etiologies, understanding the pathological process has allowed us to try to prevent illness by decreasing exposure to factors that increase risk and by screening for early signs of disease. It has also allowed us to offer treatment that can improve longevity. We have found that delay in treatment leads to end-organ damage and complications across the body.

In psychiatry, discussions of the possible impact of delayed treatment on psychosis prognosis started in the early 1990s. Wyatt,[1] reviewing the treatment of schizophrenia with antipsychotics, questioned whether there was something toxic about untreated psychosis that went beyond the immediate psychotic episode. This has been used to support the assertion that, similar to the rest of medicine, early intervention in the first onset of schizophrenia can improve long-term prognosis. And it has led to the development of first-episode services in many high-income countries. The aim is simple: to treat early and increase the likelihood of recovery.

A further development based on the premise that treating people early could improve prognosis has been the trial of treatment of people in the prodrome of schizophrenia. A recent Cochrane review[2] has concluded that there is some emerging evidence that this improves outcomes.

These are success stories that may have already made a difference to the lives of patients, but, if we want to continue to improve services, we need to understand how our interventions work. Our lack of understanding of the mechanisms through which lack of treatment leads to poorer outcomes may make it difficult for us to develop prevention, screening, and timely, targeted early intervention as has proved effective in diabetes. If we could answer Wyatt's question, and we knew what was toxic about untreated psychosis, we may be able to produce better treatment.

Numerous, different studies have tried to shed light on the delay in untreated psychosis and prognosis. They have measured the association between the time untreated and subsequent symptoms, cognitive problems, and changes in the brain. Mechanisms have been suggested to explain these findings. As summarized by Rund,[3] Wyatt[1] believed that untreated psychosis was biologically toxic to the brain. Sheitman and Lieberman[4] elaborated, claiming that the inability to regulate a presynaptic dopamine release in the limbic striatum and the prolonged sensitization and overstimulation resulted in people being refractory of treatment because of structural neuronal changes. Others have postulated that active psychosis may damage neuronal connectivity,[5] while Wood et al[6] believed that the impacts were through stress and the release of stress-related hormones.

The focus for pathological deliberations, so far, has been very much on the brain. This flies in the face of increasing reports that the etiology of psychosis is multifactorial. There are fundamental biological processes that are important for brain function, but these are significantly influenced by psychological and social factors that mediate both

brain development and subsequent brain function.[7] There are associations between genetic endowment and risk of psychosis but also factors that are linked to the development of the brain, such as childhood trauma or early separation from a parent. Cannabis increases not only the risk of psychosis but also the risk is increased in those who are born or brought up in a city. Migration increases the risk of psychosis, but some migrant groups, specifically those who are exposed to discrimination because of their race, have the highest risk. And crucially, the literature reports that such risk factors do not operate independently. They interact. The impact of biological factors, such as cannabis or genes, are significantly influenced by psychological and social factors.[7] A person's risk of developing schizophrenia relies on an interplay between biological, psychological, and social risk factors at individual and ecological levels that interact over time.[8]

It may be that not only the causation of the disorder but also the progress and prognosis have a similarly wide-ranging etiology. If we can understand the social, psychological, and biological mechanisms through which untreated psychosis is associated with outcome, we may find new avenues for improving care.

The best first-episode services instinctively offer biological, psychological, and social treatments. However, a more scientific approach would be to try to base service development on an understanding of the mechanisms through which disease progression occurs. If we knew the reasons why lack of treatment may lead to worse outcome, we may be able to develop a treatment approach based on science. This would help us to work out which treatments, deployed when, could offer the best prognosis, and whether there is a gap in our treatment repertoire.

In this In Review, we want to consider the possible mechanisms by which psychosis could be neurotoxic. The aim is to start a discussion that will allow us to build a better understanding of the processes driving outcome. Dr Kelly K Anderson and colleagues[9] from the Centre for Addiction and Mental Health have looked at postulated biological mechanisms, and Dr Ross M G Norman[10] has tried to identify social mechanisms that may link untreated psychosis with outcomes. If we can link the findings from these papers together with similar studies from our partners in psychology, we may start to develop an understanding of the impacts of untreated psychosis that will help us to improve services.

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