Two hypotheses on the high incidence of dementia in psychotic disorders

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Although schizophrenia was originally described as a neurodegenerative disorder (e.g., "dementia praecox"), most modern theories consider it a neurodevelopmental disorder. The neurodevelopmental model implies that cognitive decline precedes psychosis, a pattern that is consistent with IQ deficits among those who later develop schizophrenia. However, evidence is beginning to mount that, in addition to premorbid deficits, schizophrenia and other psychotic disorders are associated with a gradual but relentless post-onset cognitive decline that leads to dementia and premature mortality.

Longitudinal studies have found that cognition in schizophrenia and other psychotic disorders declines faster than expected due to age. A recent meta-analysis, which included over 5 million individuals and 200,000 dementia cases, reported that dementia is 2.3 times more likely in schizophrenia than in the general population.[1] Increased risk of dementia was also found in other psychotic disorders, such as bipolar disorder. Although the meta-analysis was based on data from countries with nationalized healthcare and medical record systems, these results were recently replicated in 8,011,773 US Medicare beneficiaries.[2] That analysis estimated dementia incidence is up to 11 times higher among patients with schizophrenia compared to those without serious mental illness. Indeed, the relative risk of dementia among those with schizophrenia in their late 60s is comparable to that of the general population in their late 80s. This pattern is consistent with evidence that in schizophrenia, death due to dementia is 5.2 times more common than it is in the general population.[3]

The evidence is clear that many individuals with psychotic disorders suffer from premature dementia, which robs millions of people of decades of life and health. It is imperative that we understand causes of this premature demise and prevent it. While there are many potential pathways, we highlight two testable hypotheses with strong explanatory power. If confirmed they can lead to the development of preventative measures that alleviate disease burden.

The first hypothesis is that metabolic dysfunction can lead to premature dementia in psychotic disorders. Metabolic syndrome, which encompasses obesity, dyslipidemia, and hypertension, leads to atherosclerosis, which narrows arteries in the brain and increases risk of ischemia and stroke. In the general population, metabolic syndrome predicts dementia through this pathway. Each symptom of metabolic syndrome is more prevalent in psychotic disorders than in the general population. Among those with serious mental illness, over 50% are obese, 19-39% have dyslipidemia, and 39% have hypertension.[4] Altogether, 33% meet criteria for metabolic syndrome, a rate 1.5 times that observed in the general population.[4] High rates of metabolic syndrome are attributable to various lifestyle factors associated with psychotic disorders, but also side effects of antipsychotics. People taking antipsychotic medications are nearly eight times as likely to have metabolic syndrome compared to antipsychotic-naïve patients,[4] perhaps because antipsychotics can alter insulin and glucagon release directly by acting on dopamine receptors in the pancreas.[5] In schizophrenia, metabolic syndrome is associated with greater cognitive impairment,[6] and those with serious mental illness are at increased risk of death due to cerebrovascular disease.[3] Whether metabolic syndrome leads to vascular dementia in schizophrenia is an important hypothesis that deserves investigation. If confirmed, a preventative, lifelong focus on cardiometabolic health could be employed to reduce the burden of dementia in psychotic disorders.

A second possibility is that long-term exposure to antipsychotics contributes to premature dementia. Antipsychotic exposure has been linked to worse cognition in both cross-sectional and longitudinal observational studies. These results have been confirmed in randomized controlled trials showing cognition improves when antipsychotic dosage is reduced.[7] Antipsychotics may contribute to dementia via modulation and degeneration of the mesocortical dopaminergic circuit, the same circuit underlying cognitive decline in dementia and Parkinson's disease. Schizophrenia spectrum disorders are associated with hyperactivity of dopamine function in the striatum, and hypoactivity in the rest of the brain. Antipsychotics reduce dopaminergic activity at D2 receptors, which reduces D2 signaling in

striatum, but also exacerbates hypoactivity in the prefrontal cortex. Over long periods of time, antipsychotics may impair neuronal survival in this circuit, as suggested by evidence from animal models, cell cultures, and postmortem tissue. A randomized clinical trial in psychotic depression found antipsychotics cause cortical thinning,[8] and meta-analyses find cumulative antipsychotic exposure is associated with declines in cortical grey matter. Indeed, some evidence links cortical grey matter loss to the D_2 receptor occupancy of the medication. This effect is not explained by illness duration or symptom severity, suggesting that antipsychotic exposure itself drives cortical loss. Cortical loss is, in turn, associated with cognitive decline in schizophrenia.[9] Alternatively, antipsychotics may be linked to dementia in psychosis by their anticholinergic effects. Anticholinergics have been shown to double dementia risk in the general population, and are associated with cognitive impairment in schizophrenia.[10] Overall, substantial observational evidence has linked antipsychotic exposure to cognitive and cortical changes, but more experimental evidence is needed, as it remains unclear whether these prefrontal changes are neurodegenerative, benign, or even neuroprotective. If neurodegenerative, this iatrogenic pathway may be modified by prioritizing medications that minimize such side effects.

These explanatory hypotheses of cognitive decline are not mutually exclusive. Indeed, existing evidence supports an integrative model in which poor cognitive function is the starting point of a trajectory towards dementia, proceeding via metabolic syndrome to cerebrovascular disease. Antipsychotics act on this pathway both indirectly, through effects on cardiovascular health, and directly, through cortical thinning (Figure 1). However, no study has tested this explanation. Moreover, the existing research either focused on first-episode patients, who do not have dementia, or patients recruited in old age, which excludes patients who improved, withdrew, or died, and cannot account for confounding effects of risk factors that occurred years ago. Exclusive focus on the cross-sectional studies of early stage psychotic disorders may leave us ill-equipped to help these patients in late adulthood.

Long-term longitudinal first-episode studies employing postmortem, neuroimaging, and blood-based biomarkers will be critical to understanding dementia in psychotic disorders. The current evidence indicates that schizophrenia is not only a neurodevelopmental disorder, but also a neurodegenerative one. Research and a public health strategy to preempt premature dementia in psychotic disorders is sorely needed.

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