The Long-Term Effect of Schizophrenia on the Brain: Dementia Praecox?

Kraepelin's use of the term "dementia praecox" for the condition we now know as schizophrenia encouraged the view that his patients had a progressive decline in behavioral function associated with (and probably caused by) progressive changes in brain anatomy and function over the course of illness. This view was challenged first by the failure of early postmortem histopathology studies to identify gross anatomic changes. Later, it was challenged by models proposing that neurodevelopmental alterations caused the disorder and that the primary disease-related damage to brain organization was largely in place at illness onset. Enthusiasm for "progressive" and "neurodevelopmental" models has varied over time and across countries (1), and establishing the validity of these models and their mechanisms remains one of the major challenges of schizophrenia research.

Interest in demonstrating and establishing the mechanisms for progressive disease was an important reason for several schizophrenia programs to start longitudinal studies, including MRI protocols, of "first-episode" schizophrenia more than two decades ago. In brief, they hoped to identify progressive encephalopathy that might explain a decline in function. These were very challenging studies. The 202 patients reported by Andreasen et al. in this issue (2) were recruited over 18 years and underwent scanning on average three times. Additional challenges in these studies were maintaining patients' study participation and keeping funding and investigative teams together over long follow-up periods. That 67% of the patients in this study remained involved over so long a period represents a remarkable achievement.

Patients with recurring psychosis may experience cumulative, persistent atrophic brain changes

The primary focus of the Andreasen et al. study is on clinical associations of atrophic anatomic changes with duration of persistent psychosis and intensity of antipsychotic treatment. Regional hypermetabolic activity during acute psychosis (3) and glutamate excitotoxicity (4, 5) represent potential mechanisms for a neurotoxicity of psychosis.

Indirect evidence suggests that antipsychotic medications may have adverse effects on brain anatomy and function. Persistent adverse effects of antipsychotics on some cognitive processes supported by frontostriatal brain systems are well established in preclinical models (6). Studies using similar cognitive paradigms with schizophrenia patients show similar adverse effects (7). Reduced prefrontal connectivity in resting-state fMRI studies has also been demonstrated after initiation of antipsychotic treatment (8). Thus, evidence for potential adverse effects of antipsychotics outside the domain of motor systems has grown in recent years. The greatest reason for concern about adverse neuroanatomic effects of antipsychotic treatment stems from data showing a robust reduction in brain volume in monkeys treated with clinically relevant dosages of conventional and atypical antipsychotics (9). This remains a troubling observation on clinical grounds given the lack of therapeutic alternatives to antipsychotics.

Andreasen et al. report that cortical volume loss occurs at a faster rate in schizophrenia patients than in matched healthy comparison subjects. This finding has been reported in this and other samples previously. Combined with multiple demonstrations that neuroanatomic deficits are present at illness onset, this suggests that both progressive and neurodevelopmental pathology may be important in the disorder. The apparent importance of both progressive and neurodevelopmental factors is not simplifying, but it gives us important insight into the complexity of the disorder.

Andreasen et al. also report that relapses are more common but briefer near illness onset, and that over time a subgroup of patients experience prolonged relapses. Given the data, it seems likely that this subgroup tended to show the greatest reductions in brain volume over time. Relapse duration but not number of relapses was related to brain volume changes, with the effects most prominent in the frontal lobe and white matter. This observation is consistent with the view that patients with recurring psychosis may experience cumulative, persistent atrophic brain changes—and that there may be a subgroup of patients with poor treatment response and more persistent psychotic symptoms who experience progressive neuroanatomic changes.

Antipsychotic treatment intensity was related to brain volume reductions in the frontal and temporal cortex and in parietal white matter. Antipsychotic-related effects on brain volume were notably smaller than those reported in rodent and nonhuman primate models; this difference may reflect species differences, an interaction with disease, more variable dosing clinically, or underreporting of treatment nonadherence. In any case, it is reassuring to see that progressive atrophic effects associated with antipsychotic treatment are less than those seen in animal models. Effects of relapse duration and antipsychotic treatment intensity on anatomic measures were of similar magnitude.

Questions about medication and episode effects on brain anatomy were addressed using statistical approaches that controlled for some factors using regression approaches while testing for effects of factors of interest. This approach is relatively straightforward when factors are independent, but when they are correlated, as illness severity and drug dosage are, causal inferences are less certain. It is hard to fully confirm whether sicker patients with greater brain abnormalities receive more medication (and thus the causes of anatomic changes precede or even lead indirectly to higher drug dosages), or whether brain atrophy reflects a pharmacological effect of antipsychotic drugs. The authors recognize this issue, but it is an important caveat. Other statistical issues include potential nonlinearities in the relationships of interest, such that, for example, drug dosage may be associated with brain volume reductions primarily at higher dosages or with longer relapse durations. Another question is whether a subgroup of individuals, perhaps defined by genetic or epigenetic factors, are more likely to show atrophic changes in relation to relapse duration or drug treatment intensity.

As with many advances, the findings of Andreasen et al. raise new questions. Do the volume reductions impair role function and cognition? Can preclinical studies clarify the mechanisms of antipsychotic effects on neuronal integrity? If antipsychotics are needed for symptom control and relapse prevention yet with increasing dosage there is a risk of atrophic brain changes, the need to optimize drug dosing would be increased, emphasizing lower effective dosages rather than raising dosage to the level just below a significant side effect threshold (10). This latter issue highlights the direct clinical importance of the findings from this study.

This study of a class of drugs used over 50 years highlights the still limited understanding we have of the full range of beneficial and adverse effects of antipsychotic medications. We have learned about clinical efficacy and receptor binding profiles, but the complex and longer-term effects of antipsychotic drugs on functional brain systems and the systems-level neurobiology of psychosis remain far from clear. Armed with a fuller understanding, we could be better positioned to develop new treatments that maximize benefits and minimize adverse effects and be better able to talk to patients and families about long-term treatment options.

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Dr. Sweeney has served on advisory boards for Bristol-Myers Squibb, Eli Lilly, Pfizer, Roche, and Takeda and has received grant support from Janssen. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.