Methodological Successes and Limitations in a Randomized, Delayed-Start Study Comparing Oral and Injectable Antipsychotics (DREaM)

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SUBMISSION DETAILS

What is the Methodological Question Being Addressed? In order to inform future trials, we sought to understand the limitations of a novel clinical trial design used in a randomized, delayed-start study comparing treatment with long-acting injection (LAI) versus oral antipsychotics (OAPs) in patients with recent-onset schizophrenia. Specifically, was the study duration sufficient? Were the chosen endpoints and assessments optimal? Was the frequency of visits appropriate? Did the re-randomization procedure work?

Introduction Disease modification—the slowing, halting, or reversing of disease progression—represents a primary therapeutic aim for many chronic, progressive diseases. Given the chronicity of schizophrenia, which often has poor outcomes with existing treatments, demonstrating beneficial effects of early introduction of LAIs remains an important goal. We therefore designed a modified delayed-start study to evaluate disease modification in patients with recent-onset schizophrenia (DREaM; NCT02431702). We report the unique study design, key innovations, and learnings from DREaM, which evaluated if early introduction of an LAI modifies disease course compared with OAPs in patients with recent-onset schizophrenia.

Methods Traditional randomized delayed-start designs have significant limitations and therefore require extensive knowledge of the disease under study and application of rigorous statistical approaches. To address limitations associated with delayed-start trials, the DREaM study design included a run-in period to establish treatment tolerability and provide a basis for a matched control rerandomization. A second randomization step generated groups that were comparable with respect to disease characteristics and minimized confounding bias. The objective of this design was to evaluate if postponement of LAI initiation resulted in different outcomes than LAI initiation earlier in the disease course.

Results DREaM enrolled 273 patients with recent-onset schizophrenia or schizophreniform disorder into Part I. Two hundred and thirty-five patients were randomized in Part II, and 169 patients were randomized in Part III. During the initial run-in period (Part I), most patients showed marked improvement in clinical symptoms, resulting in a large, persistent study effect. After Part I, patients who continued with the study improved by 1 unit (median change) in Clinical Global Impression-Severity score and by 8.4 points (mean change) in Personal and Social Performance scale total score. This prolonged study effect did not allow differentiation of treatment during the first 9 months. Predicted differences between study groups only became evident after ~1 year.

Conclusion Results suggest that a longer treatment period would have been necessary in this trial

to demonstrate a putative differential effect on disease progression between LAI and OAPs. Inherent biases of randomized controlled trials, requirements for caregiver involvement, and interactions with study personnel at specialized first episode clinics may have increased overall compliance with both treatment approaches, such that expected real-world differences in treatment compliance were not evident during the different treatment periods in this study. Nevertheless, after 1 year, the study effect began to diminish and treatment differentiation for major end points was evident. These results suggest that to be successful, future trials must reduce the study effect with more prolonged treatment periods and/or more pragmatic designs.

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Guidelines I have read and understand the Poster Guidelines

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