Improving Outcomes in Schizophrenia—A Case for Initiation of Long-Acting Antipsychotics in Early-Phase Illness

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The reduction of adverse outcomes is of crucial importance in schizophrenia, a relapsing and remitting chronic illness with a 13- to 15-year reduction in life expectancy. The recurrence of acute psychotic symptoms after a period of recovery is often highly distressing to individuals with schizophrenia and is associated with a reduced response to antipsychotic treatment. The prevention of relapses of acute psychosis and psychiatric hospitalizations early in the course of illness has major prognostic implications in schizophrenia and related psychotic disorders.

In a case series study of 70,396 individuals with schizophrenia, Wei et al found a lower risk of suicide attempts, all-cause hospitalizations, and psychiatric hospitalizations associated with long-acting injectable antipsychotic (LAIA) treatment compared with oral antipsychotic (OA) treatment. Furthermore, Wei et al also demonstrated a lower risk of extrapyramidal symptoms and fewer hospitalizations for cardiovascular diseases and for somatic disorders during LAIA treatment compared with OA treatment. There was an increase in the risk of extrapyramidal symptoms among elderly individuals within the first 90 days of LAIA treatment. By using a self-controlled case series design in which individuals act as their own control, the authors mitigated the effect of fixed confounders that do not change over time. Furthermore, with a mean (SD) duration of follow-up of 12.5 (4.7) years, this case series study informs our understanding of the long-term tolerability and effectiveness of LAIA treatment in improving longitudinal outcomes among people with schizophrenia.

The study by Wei et al adds to an existing body of work supporting both the safety of LAIAs and the superior effectiveness of LAIA treatment compared with OA treatment in reducing hospitalizations for acute psychosis among individuals with schizophrenia. A 2021 systematic review and comparative meta-analysis by Kishimoto et al that included 397,319 patients found no significant differences in the risk of extrapyramidal symptoms and most adverse events between LAIA and OA treatment. Furthermore, the review by Kishimoto et al demonstrated an increased effectiveness of LAIAs vs OAs in reducing the risk of psychiatric hospitalization, and the summary effect size was largest in pre-post studies, which the authors suggest is due to differences in study populations across the included study designs. For example, patients who both qualify for and volunteer to participate in a randomized clinical trial (RCT) are typically more adherent to treatment at baseline, which would attenuate the ability of RCTs to capture differences in outcomes between LAIAs and OAs. Furthermore, the highly selective inclusion criteria of many RCTs may also exclude clinical subgroups of patients with schizophrenia based on demographic or clinical factors associated with nonadherence, such as active substance use. Wei et al performed subgroup analyses on the safety and effectiveness of LAIAs among several patient groups that are not highly represented in RCTs, such as the elderly, individuals living with comorbid substance use disorders, and individuals early in the course of psychotic illness.

Perhaps the most clinically relevant findings of the study by Wei et al are the significant prognostic advantages associated with the initiation of an LAIA within the first 2 years of diagnosis of schizophrenia. The authors found that initiation of an LAIA during the first 2 years of illness was associated with a greater reduction in all-cause emergency department visits, all-cause hospitalizations, and psychiatric hospitalizations during the full treatment period compared with later LAIA initiation. Previous work examining the effectiveness of LAIAs in reducing hospitalizations...
in early-phase psychosis has had mixed results. However, several larger RCTs have demonstrated a benefit of LAIA treatment in reducing hospitalization in early-phase illness. For example, a multisite RCT of 489 individuals with schizophrenia with less than 5 years of lifetime antipsychotic exposure found treatment with once-monthly long-acting injection of aripiprazole to be associated with a significant delay in time to initial psychiatric hospitalization during the 2-year follow-up period compared with treatment as usual.

The reduction in suicide attempts observed by Wei et al during LAIA treatment compared with OA treatment has critical implications for reducing the mortality gap among individuals living with schizophrenia and other related disorders. Individuals with schizophrenia are at a heightened risk of death by suicide compared with the general population. The increased risk of suicide may be highest early in the course of illness, specifically the year after initial psychiatric hospitalization. Wei et al demonstrated an overall reduction in suicide attempts associated with LAIA treatment compared with OA treatment. Furthermore, LAIA treatment initiation within the first 2 years of onset of illness was associated with a more significant reduction in suicide attempts compared with later LAIA initiation. These findings regarding decreased rates of suicide support the findings from a 2021 cohort study demonstrating an association between LAIA treatment and lower all-cause mortality and risk of suicide attempts compared with OA treatment among patients newly diagnosed with schizophrenia. Taken together, the results from these studies are of significant clinical importance because the heightened risk of suicide after a first episode of psychosis remains a critical public health problem.

The association between LAIA treatment and reduced risk of suicide attempts and psychiatric hospitalization demonstrated in the study by Wei et al supports the role of LAIAs as an important tertiary prevention strategy in schizophrenia. Emerging evidence supports the initiation of LAIAs within the first 2 years of illness to alter the disease trajectory in this chronic and often disabling illness, but further study across geographic regions and patient populations is needed. Given the significant prognostic implications, there is a critical need for additional research in populations experiencing a first episode of psychosis to explore the use of LAIA as a first-line pharmacologic treatment, regardless of the perceived level of adherence to an OA. Further research on the effectiveness and tolerability of individual LAIA formulations in early psychosis is essential to guide shared decision-making between clinicians and patients during the critical early years of psychotic illness.

ARTICLE INFORMATION

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REFERENCES


