Individuals with schizophrenia spectrum disorders (SSDs) die 13 to 15 years earlier than the general population. The mortality gap in SSDs has persisted over the past several decades despite advancements in psychiatric and other forms of medical care. The mortality disparity in SSDs is driven in part by disproportionately high rates of cardiometabolic disease, nicotine use, and death due to suicide and accidents among individuals with SSDs. Both the persistent mortality gap and the heterogeneity in the course of illness of SSDs suggest a need for a shift toward tailoring first-episode psychosis (FEP) treatment based on both shared decision-making and the risk of adverse outcomes. Using a risk stratification method to guide psychiatric treatment is similar to approaches used in other specialties, such as cardiology and oncology, that use risk prediction tools to personalize treatment based on prognostic factors. A similar risk stratification approach is crucial to reducing the mortality gap in SSDs.

Validated risk stratification techniques to guide pharmacologic management are critically needed in the FEP population in particular, given the substantially heightened risk of premature death in the first 2 to 3 years of psychotic illness. Among individuals with SSD across the lifespan, the absolute and relative risk of mortality due to suicide is highest among young adults. In their recent work, Lieslehto et al leveraged machine learning to develop a novel prediction model (available online as MIRACLE-FEP) to estimate the risk of premature mortality following the onset of psychotic illness. Using national registry data, the machine learning model was calibrated to predict 2-year mortality in a sample of 20,000 Swedish patients with FEP. The most influential variables in the discovery model (ie, based on feature gain) included comorbid substance use disorders (SUDs), age, number of previous somatic hospitalizations, length of first hospitalization for psychosis, and male sex. The model was retrained using these variables and then validated in a Swedish sample of 4052 patients with FEP and a Finnish sample of 1490 patients with FEP.

The model had satisfactory predictive performance (area under the receiver operating characteristic curve [AUROC] of 0.71 in the discovery sample). As noted by Lieslehto et al, the discriminative performance of the discovery model is similar to other widely used predictive tools in medicine, such as the performance of the Framingham Risk Score, in which performance varies globally in external validation samples (AUROC, 0.62-0.88). This new model must be validated in other populations, particularly in health care systems with shorter median psychiatric hospitalization stays, in countries without universal health care, in low-income countries, and among diverse racial and ethnic populations. Furthermore, given the potential prognostic benefits in FEP, other validated risk prediction tools are needed to predict outcomes such as treatment disengagement, rehospitalization, and other clinical outcomes.

To our knowledge, Lieslehto and colleagues are among the first to demonstrate the potential clinical utility of risk stratification in guiding antipsychotic selection in early psychosis. Without risk stratification, of the included antipsychotics, oral risperidone, oral aripiprazole, and long-acting injectable (LAI) antipsychotics were associated with a reduction in 15-year mortality in the discovery sample (54%, 51%, and 36% reduction in mortality compared with no antipsychotic, respectively). Following risk stratification with the model, only oral risperidone and aripiprazole were associated with significantly reduced 15-year mortality risk in the predicted-to-survive cohort. Among patients predicted to die by the model, only LAI antipsychotic medications and mood stabilizer treatment were significantly associated with reduced risk of 15-year mortality (with a 55% and 36% reduction in mortality, respectively). The varying benefit of LAI antipsychotics and oral second-generation...
antipsychotics (SGAs) between the predicted-to-die and predicted-to-survive groups supports the potential clinical utility of risk stratification in FEP.

The work by Lieslehto and colleagues adds to a growing body of evidence supporting the role of LAI antipsychotics in reducing the risk of mortality in SSDs among individuals at high risk of premature death. A recent systematic review and meta-analysis of observational cohort studies found second-generation LAI antipsychotics were associated with a 61% reduction in relative all-cause mortality risk, which was the largest reduction in all-cause mortality risk of any antipsychotic subgroup. In a register-based cohort study of more than 29,000 individuals with schizophrenia, second-generation LAI antipsychotics were associated with an 85% reduction in mortality risk in the early psychosis group compared with no antipsychotic treatment. Compared with equivalent oral antipsychotic formulations, second-generation LAI antipsychotics were associated with a 33% reduction in all-cause mortality risk in the total cohort in pairwise comparisons. The estimated reduction in absolute risk of mortality associated with second-generation LAI antipsychotic use may be as much as 10% over a 15 to 20-year period. The protective effect of second generation LAI antipsychotics vs oral equivalents may be commensurate with other widely used secondary prevention strategies in medicine. For example, although not directly comparable due to differences in baseline risk of all-cause mortality, the statin class of medications, a widely used primary and secondary prevention tool in medicine, has been associated with a 9% reduction in relative risk and a 0.8% reduction in absolute risk of all-cause mortality compared with placebo or usual care.

The protective effect of second-generation LAI antipsychotic treatment supports the need for LAI antipsychotics to be used proactively rather than reactively in FEP, especially among patients with other risk factors for premature mortality. This model and meta-analytic evidence suggest that patients with SSD and co-occurring SUD are among the patients at the highest risk of premature mortality following the onset of psychotic illness. Since both SUDs and antipsychotic nonadherence behaviors are highly prevalent among individuals with FEP in many areas of the world, inpatient and outpatient psychiatrists should systematically include LAI antipsychotics in shared decision-making discussions after an FEP. Delaying offering LAI antipsychotics until the first clinician-identified period of nonadherence likely contributes to undue morbidity and a heightened risk of premature mortality in the early psychosis period. LAI antipsychotics are also often favorable options for patients, regardless of adherence history or premature mortality risk, due to lifestyle factors such as eliminating daily oral medications, less frequent medication monitoring by family or other caregivers, and removing the need to store oral medications in shared living spaces such as dormitories. Furthermore, early LAI antipsychotic treatment in FEP can expedite the identification of treatment-resistant schizophrenia (TRS) due to ensured adherence. Improvements in early recognition of TRS and reductions in the time to transition to clozapine are also needed to reduce the mortality gap in schizophrenia. A major limitation of the present work by Lieslehto and colleagues is the exclusion of clozapine, an SGA associated with a reduction in all-cause mortality and the gold standard treatment in TRS. Future studies investigating this and other risk stratification tools to guide treatment to reduce the risk of premature mortality in SSDs should include clozapine treatment.

The new prediction model by Lieslehto et al must be validated in other populations before guiding clinical decision-making. However, the heterogeneity in treatment effectiveness by risk strata in this work underscores the importance of using a personalized approach to pharmacologic treatment selection in FEP that is individualized to a patient’s risk factors and treatment preferences.
REFERENCES


