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GUEST EDITORIAL

Real-world evidence on antipsychotics may improve schizophrenia treatment

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The introduction of rigorous clinical trial standards into psychiatry began with the advent of the "psychopharmacology revolution." The first double-blind trial in psychiatric patients was published in 1954, featuring chlorpromazine (1), and one of the earliest well-designed randomized clinical trials (RCTs) was also published that year using lithium (2). By 1955, the parallel-group design had been introduced into psychiatry (3), and in 1964, the first large, multicenter, double-blind, randomized, placebo-controlled trial involving chlorpromazine was published (4). Psychiatry thus joined other fields of medicine in the rapid development of pharmacological treatments and trial designs. Relevant statutes and regulations were introduced to ensure that investigational drugs met efficacy and safety standards through adequate and well-controlled clinical trials (5, 6). Double-blind RCTs remain the gold standard for testing investigational drugs for the treatment of schizophrenia and serve as the highest level of evidence for clinical guidelines demonstrating treatment effectiveness (7). Over the past two to three decades, the number of real-world studies (RWS) has grown substantially. These include observational studies, such as the SOHO (Schizophrenia Outpatient Health Outcomes) studies (8), as well as randomized "pragmatic" trials like EUFEST (European First Episode Schizophrenia Trial) (9). This trend has continued with the emergence of studies based on large-scale, often nationwide, digitized healthcare data (10). With the increasing availability of well-documented real-world data (RWD) from various regions, a central question has arisen: how can RWD support drug development? Regulatory agencies such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have issued multiple guidance documents outlining how to collect, analyze, and utilize RWD and real-world evidence (RWE) in the context of drug development and approval.

A further logical question is how the results of RCTs translate into real-world clinical practice. A meta-analysis concluded that the effectiveness findings of RWS on antipsychotics in schizophrenia are consistent with those of RCTs (11). This finding was further supported by a large network meta-analysis conducted by another group (12), which concluded: "...antipsychotic between-drug comparison findings for the outcome of relapse prevention might be portable from RCTs to the real world."

Analyses of RWD have also highlighted important limitations of RCTs, particularly in the case of long-acting injectable (LAI) antipsychotics. A large systematic review and comparative meta-analysis by Kishimoto et al. (13) reported small summary effect sizes in both RCTs and cohort studies. However, the study concluded that "LAIs showed a consistent benefit over oral antipsychotics in all study designs regarding hospitalization or relapse, and in many other outcomes related to efficacy and effectiveness." Similarly, a study by Katona et al. (11) demonstrated the superiority of LAI risperidone over oral risperidone when using time to all-cause discontinuation as a measure of efficacy/effectiveness, as illustrated in Figure 1.

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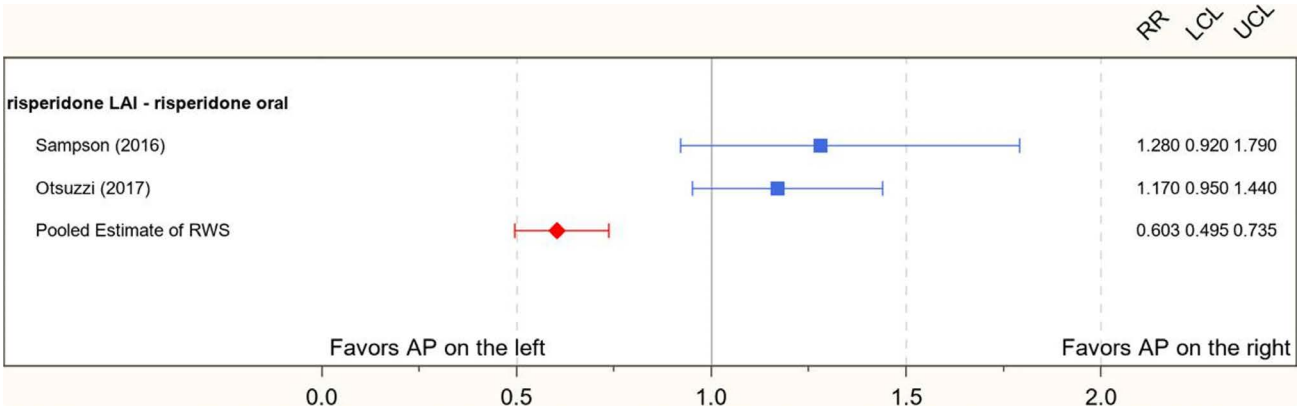

Figure 1. Effect size estimates from previously published meta-analyses of RCTs (blue) and from our meta-analysis of real-world studies (red). RR relative risk, LCL lower confidence limit, UCL upper confidence limit [Adapted from Katona et al. (11)].

The current body of evidence from RWD on antipsychotic treatment supports its integration into clinical practice (14). Incorporating RWD into clinical guidelines and decision-making processes may improve real-world outcomes in schizophrenia. However, achieving this goal will require consensus on guideline development methodology. This editorial also serves as a call to publish more real-world data from different countries, as treatment effectiveness may vary by region.

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