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Editorial

Real-world effectiveness of antipsychotics

There are two fundamental questions concerning the antipsychotic treatment of schizophrenia. First, is the overall effect of treatment positive; that is, does efficacy outweigh the adverse effects? Second, are there any clinically meaningful differences between specific antipsychotic agents?

Although a large body of randomized controlled studies (RCTs) has shown that antipsychotics are highly effective in reducing symptoms and improving quality of life during short-term interventions, it has been suspected that the use of antipsychotics in long-term treatment may lead to brain atrophy (1) or a lower rate of recovery (2). Furthermore, it has been suggested that adverse effects such as weight gain would contribute significantly to excess mortality seen among patients with schizophrenia. There are several reasons why RCTs have not been able to solve this overall risk-benefit question. For example, the patients included in RCTs represent a small atypical minority of the patient population, as up to 80–90% of patients are excluded because of mental or physical comorbidity, suicidal or antisocial behaviour, or substance abuse (3). Another reason is that thousands of patients and follow-up periods of several years are required to achieve enough statistical power to study relatively infrequent phenomena such as suicide or death, or the incidence of severe physical illness. Observational studies can overcome these obstacles by using nation-wide electronic databases of hospitalization, mortality, and filled prescriptions. In this issue of the Journal, Vanasse et al. (4) report results on the comparative effectiveness of antipsychotic drugs in schizophrenia. The authors used administrative databases from Quebec province in Canada, which included more than 18 000 patients who started to use an antipsychotic from 1998 to 2005. Their results showed that using any antipsychotic drug was associated with a lower risk of mental and physical health events (i.e., suicide, any death, hospitalization, or an emergency hospital visit due to a mental or physical disorder), when compared to no use of an antipsychotic. This result is in line with previous large cohort studies that have included mainly chronic patients (5–10). It is rather reassuring that all seven large cohort studies published thus far indicate that the use of antipsychotics is associated with a lower risk of death or severe health problem when compared with no use. This suggests that antipsychotics do more good than harm.

The other main finding by Vanasse et al. is that there are clinically meaningful differences in the overall effectiveness of antipsychotics. Clozapine was associated with best outcome, even when mortality and physical health events were included in the primary outcome measure. This is in agreement with four previous studies that suggest that clozapine use is associated with a lower risk of death, when compared to other treatments (7, 11–13). Also, olanzapine performed better than first-generation antipsychotics, but quetiapine was associated with a worse outcome. These findings were also reported previously in prevalent-user cohorts (6, 7). Thus, results from different cohorts, from different countries, show rather consistent results.

Although observational studies have important advantages, such as non-selected representative study populations, long follow-up periods, and high statistical power, they also have some shortcomings. The most important limitation is selection bias. For example, old patients are more likely to receive first-generation drugs, while younger patients receive more novel medications. If the age difference is not adjusted, the results on mortality will be severely distorted. Even if the most important covariates such as sex, age, age at illness onset, duration of illness, number of previous hospitalizations, physical illness, and history of suicidal behaviour were adjusted, there always remains residual confounding. One way to overcome this problem is to use within-individual analysis, in which each individual is his or her own control. In this approach, the exposure periods of each individual are compared with the non-exposure periods of the same individual. Therefore, the only factors which

need to be adjusted are those that change as a function of time. These factors include the calendar age of the patient, temporal order of exposure periods, and concomitant other medication. For example, the use of antidepressants and benzodiazepines is common among patients with schizophrenia, and these concomitant medications may have a substantial impact on mortality, for example (9). It is somewhat surprising that no studies on the real-world effectiveness of antipsychotics have used within-individual analysis this far, expect the one by Walker et al. (13). Even so, many of the main results of previous observational studies are unlikely to be explained by selection bias. For example, patients using clozapine are typically the most suicidal and severely ill patients, with the highest number of previous re-hospitalizations, and with the highest intrinsic risk of relapse. Therefore, we may assume that the superior outcome associated with clozapine is diluted, rather than enhanced, due to a selection bias and residual confounding.

Another issue is the accuracy of the exposure definition. Thus far, this methodological procedure has received little attention. The most widely used methods for defining exposure periods have been fairly simplistic such as fixed time windows (e.g., 90 or 180 days from purchase order), or an assumption that all patients use one defined daily dose (DDD) per day. However, such procedures may lead to inaccurate definitions of drug exposure, and more valid methods giving better estimates are needed. For example, a novel PRE2 DUP method constitutes drug use periods from the purchase histories of each individual, making it possible to achieve substantially more accurate exposure periods than traditional methods (14).

What are the practical clinical implications of the study by Vanasse et al.? The results from this new-user cohort confirm the previous results from prevalent-user cohorts, indicating that clozapine and olanzapine are associated with a better outcome and quetiapine with worse outcome than first-generation antipsychotics (6, 7). The study also confirms previous results from prevalent and new-user cohorts (5–10), which conclude that antipsychotic use is associated with a lower risk of death when compared with no use. The effect sizes of the observed differences were moderately large, indicating that they are clinically meaningful. Since the study was able to compare both apples (i.e., the risk of mental health events reflecting efficacy) and oranges (i.e., the risk of physical health events reflecting tolerability) at the same time, the results provide a rather comprehensive view for the overall effectiveness of these treatments and the patients' wellbeing. Therefore, one can easily agree with the main conclusion of the study, which states that international public health and drug agencies should start surveillance of real-world antipsychotic treatment outcomes, to provide essential information for schizophrenia treatment guidelines.

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