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Long-Term Real-World Effectiveness of Pharmacotherapies for Schizoaffective Disorder

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Objective: **To investigate the long-term real-world effectiveness of antipsychotics and other psychopharmacotherapies in the treatment of schizoaffective disorder (SCHAFF).** ***Method:*** **Two nationwide cohorts of SCHAFF patients were identified from Finnish and Swedish registers. Within-individual design was used with stratified Cox regression. The main exposure was use of antipsychotics. Adjunctive pharmacotherapies included mood stabilizers, antidepressants, and benzodiazepines and benzodiazepine-related drugs. The main outcome was hospitalization due to psychosis.** ***Results:*** **The Finnish cohort included 7655 and the Swedish cohort 7525 patients. Median follow-up time was 11.2 years (IQR 5.6–11.5) in the Finnish and 7.6 years (IQR 3.8–10.3) in the Swedish cohort. Clozapine and long-acting injectable (LAI) antipsychotics were consistently associated with a decreased risk of psychosis hospitalization and treatment failure (psychiatric hospitalization, any change in medication, death) in both cohorts. Quetiapine was not associated with a decreased risk of psychosis hospitalization. Mood stabilizers used in combination with antipsychotics were associated with a decreased risk of psychosis hospitalization (Finnish cohort HR 0.76, 95% CI 0.71–0.81; Swedish cohort HR 0.84, 0.78–0.90) when compared with antipsychotic monotherapy. Combination of antidepressants and antipsychotics was associated with a decreased risk of psychosis hospitalization in the Swedish cohort (HR 0.90, 0.83–0.97) but not in the Finnish cohort (1.00, 0.94–1.07), and benzodiazepine use was associated with an increased risk (Finnish cohort HR 1.07, 1.01–1.14; Swedish cohort 1.21, 1.13–1.30).** ***Conclusions:*** **Clozapine, LAIs, and combination therapy with mood stabilizers were associated with the best outcome and use of quetiapine and benzodiazepines with the worst outcome in the treatment of SCHAFF.**

Key words: psychiatric hospitalization/antipsychotics/mood stabilizers/antidepressants/benzodiazepines

Introduction

Schizoaffective disorder (SCHAFF) is a common diagnosis in psychiatry, even though the nosological status of SCHAFF remains controversial.[1,2] SCHAFF symptoms include both schizophrenic (hallucinations, delusions) and affective (depression, mania) symptoms[3] and both ICD-10 and DSM-5 separate manic/bipolar and depressive subtypes of SCHAFF.[4,5] ICD-11 aims to improve the differential diagnosis and diagnostic accuracy of SCHAFF.[6] It has been debated whether SCHAFF represents an independent illness, an atypical form of schizophrenia or a mood disorder, a form of schizophrenia combined with a mood disorder, a heterogeneous group of both schizophrenia and mood disorder patients, or if SCHAFF is on the continuum of schizophrenia and mood disorder spectrum.[1] A systematic review and meta-analysis concluded that SCHAFF may be closer to schizophrenia than bipolar disorder but it shares features of both disorders.[7] Also, from a genetic perspective, SCHAFF seems to be related to both bipolar disorder and schizophrenia.[8] Conducting formal meta-analyses and giving specific guidelines for SCHAFF pharmacotherapy have been challenging due to the small number and heterogeneity of studies focusing purely on SCHAFF patients.[9–11] Pharmacotherapy recommendations for SCHAFF are

mostly derived from studies on schizophrenia and bipolar disorder, and thus patients with SCHAFF are commonly treated with antipsychotics, mood stabilizers, and/or antidepressants.[3,9,12] Of specific antipsychotics, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved the use of paliperidone for SCHAFF.[10,13] Combining antipsychotics with adjunctive psychopharmacotherapies, namely mood stabilizers and/or antidepressants, in SCHAFF is common compared with schizophrenia[14,15] and bipolar disorder.[14]

This study compares the long-term real-world effectiveness of psychopharmacotherapies for SCHAFF in two nationwide cohorts in order to observe whether the results are consistent in both countries, indicating that they may be generalizable to other populations as well. Sixteen most commonly used antipsychotics in both countries were reported, and drug formulation information was utilized to further categorize antipsychotics to oral and long-acting injectables (LAIs). Other pharmacotherapy categories included mood stabilizers, antidepressants, benzodiazepines and benzodiazepine-related, so-called Z-drugs (BZDR).

Methods

Study Population

A detailed description of the study population can be found in the Supplementary Appendix. Two cohorts of persons with SCHAFF identified from Finnish and Swedish nationwide registers were utilized for this study. In both countries, all residents have been assigned a unique personal identification number which was utilized in the linkage of country-specific registers.

The base of the Finnish cohort has been described previously.[16] It included all persons treated due to schizophrenia (the International Classification of Diseases [ICD-10] code F20) and SCHAFF (F25), with corresponding ICD-8 and-9 codes (295*), in inpatient care in Finland as recorded in the Hospital Discharge Register (HDR) maintained by the National Institute of Health and Welfare. The cohort included 7655 persons with SCHAFF.

The Swedish study base included all persons aged 16–64 with schizophrenia spectrum disorder diagnoses (ICD-10 F20, F25) and a registered treatment contact between July 1, 2005 until December 31, 2013 in Sweden.[17] The diagnoses were derived from inpatient and specialized outpatient care registers (the National Patient Register [NPR], maintained by the National Board of Health and Welfare) and disability pensions and sickness absences from the MiDAS register (maintained by the Swedish Social Insurance Agency). The cohort included 7525 persons with SCHAFF.

For both cohorts, the follow-up started on July 1, 2006. The follow-up time ended at death, change of diagnosis to schizophrenia (F20), or the end of the study (December 31, 2016 for the Swedish cohort and December 31, 2017 for the Finnish cohort), whichever occurred first. The different follow-up windows for the cohorts were due to reasons of registry data availability.

Exposure

The main exposure measure was use of antipsychotics, which were defined as Anatomical Therapeutic Chemical (ATC) classification codes N05A (lithium N05AN01 excluded). In addition to drug substance level marked by ATC code, drug formulation information was utilized to further categorize antipsychotics into orals and LAIs. Most common antipsychotic monotherapies were assessed and all exposure periods including two or more antipsychotics used concurrently were defined as "polytherapy."

Adjunctive pharmacotherapy categories included mood stabilizers (carbamazepine N03AF01, valproic acid N03AG01, lamotrigine N03AX09, lithium N05AN01), antidepressants (N06A), and BZDRs (N05BA, N05CD, N05CF).

Drug use periods, ie, when drug use started and ended, were constructed with the PRE2DUP method which is based on a sliding average of defined daily doses (DDDs), purchase dates, amounts of drugs dispensed, and personal drug use patterns.[18] Each drug for each person was modeled separately, and oral antipsychotics and LAIs were also separated.

Outcomes

The main outcome measure was hospitalization due to psychosis (ICD-10 codes F20–F29), used as a marker for relapse. In addition, we analyzed a composite measure of treatment failure, including psychiatric hospitalization, any change in medication (switch, discontinuation, addition), and death. We also conducted a sensitivity analysis where the outcome was defined as any psychiatric hospitalization (ICD-10 codes F00–F99). In the analyses, an individual may have had recurring outcomes (except death).

Statistical Analyses

The analyses were conducted separately in the Finnish and Swedish cohorts using within-individual design.[19] In this design, each individual formed their own stratum. All time-invariant covariates (such as sex) were controlled for in the design and analyses were adjusted for time-varying covariates, ie, sequential order of treatments, use of other pharmacotherapies (mentioned in the exposure section), and time since cohort entry. Main analyses were performed using stratified Cox regression models yielding hazard ratios (HRs) and 95% confidence intervals (CI). Sensitivity analyses were conducted in between-individual

design and analyzed with the traditional Cox model by adjusting for factors presented in supplementary table 1.

When comparing the effectiveness of specific antipsychotics, the reference was nonuse of antipsychotics. As antipsychotics are considered the first-line treatment, other medication categories were considered to be adjunctive therapies. These adjunctive pharmacotherapies were analyzed with antipsychotic use serving as reference (without adjunctive use). The results are reported for the combination of antipsychotics used concomitantly with certain adjunctive pharmacotherapies. This was done to observe whether combination use (which potentially has more adverse effects) has superior real-world effectiveness compared with antipsychotic only use. For antipsychotics, 16 most commonly used antipsychotics (in both countries) were reported (namely [oral if not otherwise specified] olanzapine, olanzapine LAI, clozapine, quetiapine, risperidone, risperidone LAI, aripiprazole, aripiprazole LAI, perphenazine, perphenazine LAI, paliperidone LAI, haloperidol, haloperidol LAI, zuclopenthixol, zuclopenthixol LAI, and levomepromazine) in addition to other second-generation (SG) antipsychotics, whereas other first-generation (FG) category was left out due to sparsity of users. In addition to monotherapies, polytherapy (more than one antipsychotic used concomitantly) was reported as an exposure for the main outcome. Categorization into FG-oral, FG-LAI, SG-oral, and SG-LAI is presented in supplementary table 2.

Five most commonly used oral antipsychotics (clozapine, olanzapine, quetiapine, risperidone, aripiprazole) and SG-LAIs as a category were analyzed in combinations with adjunctive pharmacotherapies. In these analyses, monotherapy of a specific antipsychotic was used as a reference to which that specific antipsychotic combined with an adjunctive pharmacotherapy class was compared with (eg, olanzapine monotherapy was used as a reference for olanzapine-mood stabilizer analyses). The results are presented as adjusted HRs with 95% CIs.

It was ensured that persons with uncertainty of diagnosis were removed. In the main analyses, individuals appeared in the analyses up until they received a diagnosis of schizophrenia, after which they did not contribute to data anymore. In the sensitivity analyses, anyone who received a schizophrenia diagnosis at any point during their follow-up was completely excluded from the analyses.

Nominal *P* values are displayed throughout the text, unless otherwise stated. *P* values were corrected for multiple comparisons using the Benjamini-Hochberg false discovery rate on a per graph basis and corrected *P* values <.05 were considered statistically significant.

Permissions were granted by pertinent institutional authorities at the Finnish National Institute for Health and Welfare (permission THL/847/5.05.00/2015), the Social Insurance Institution of Finland (65/522/2015), and Statistics Finland (TK53-1042-15). The Regional Ethics Board of Stockholm approved the Swedish part of this research project (decision 2007/762-31).

Results

In both cohorts, approximately 60% of the patients with SCHAFF were females (60.2% in the Finnish and 60.5% in the Swedish cohort) (supplementary table 3). Mean age was also of similar range, 46.7 years (SD 14.6) in the Finnish cohort and 45.1 years (SD 12.1) in the Swedish cohort. During the follow-up, 13.1% of the Finnish cohort and 22.4% of the Swedish cohort were censored due to change of diagnosis into schizophrenia.

Median follow-up time was longer in the Finnish cohort (11.2 years, IQR 5.6–11.5) than in the Swedish cohort (7.6 years, IQR 3.8–10.3). During the follow-up, 50.5% of the Finnish and 46.2% of the Swedish cohort had psychosis hospitalization, and corresponding figures for any psychiatric hospitalization were 57.9% and 54.7%, respectively. In both cohorts, 93%–94% used antipsychotics during the follow-up and FG-use was generally more common in Sweden, whereas clozapine and antipsychotics polytherapy were more common in Finland (supplementary table 3). Concurrent antidepressant and antipsychotic use was more frequent in the Swedish cohort (56% of the Swedish vs 49% of the Finnish cohort), whereas use of mood stabilizers was more common in the Finnish cohort (41% of the Swedish, 47% of the Finnish cohort). BZDRs were the most common adjunctive pharmacotherapy in both countries, used by 72% of Swedish and 61% of the Finnish cohort.

Clozapine, LAIs, and antipsychotic polytherapy were consistently associated with a decreased risk of psychosis hospitalization in both cohorts (figure 1). Quetiapine was not associated with a decreased risk as compared with nonuse of antipsychotics in either country. Exposure to aripiprazole LAI or levomepromazine was associated with a decreased risk in the Finnish cohort, but not in the Swedish cohort.

When all persons who were diagnosed with schizophrenia during the follow-up (ie, diagnosis was changed) were removed from the analyses, the results remained similar (supplementary figures 1 and 2). Between-individual analyses had a rather similar rank order for antipsychotics as the main analyses (supplementary figures 3 and 4). Clozapine and LAIs were also associated with the lowest risk of treatment failure (figure 2). Of all antipsychotics, only use of levomepromazine was associated with an increased risk of treatment failure in the Swedish cohort.

Use of mood stabilizers in combination with antipsychotics was associated with a 24% (HR 0.76, 95% CI 0.71–0.81, Finnish cohort) and 16% (HR 0.84, 0.78–0.90, Swedish cohort) decreased risk of psychosis

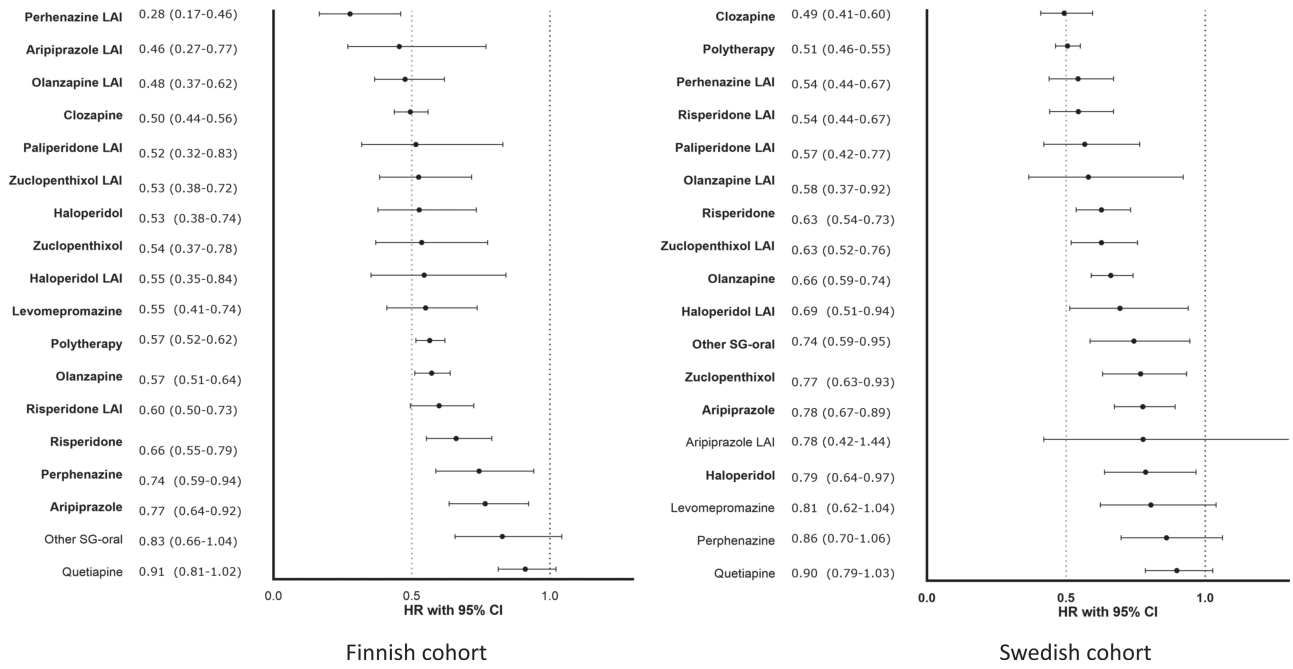

Fig. 1. Relative hazard of psychosis hospitalization (hazard ratio [HR], with 95% confidence interval [CI]) associated with specific antipsychotics in schizoaffective disorder (SCHAFF) compared with no use of antipsychotics, within-individual comparisons. In bold are depicted agents that are significant after Benjamini-Hochberg correction for 5% false discovery rate.

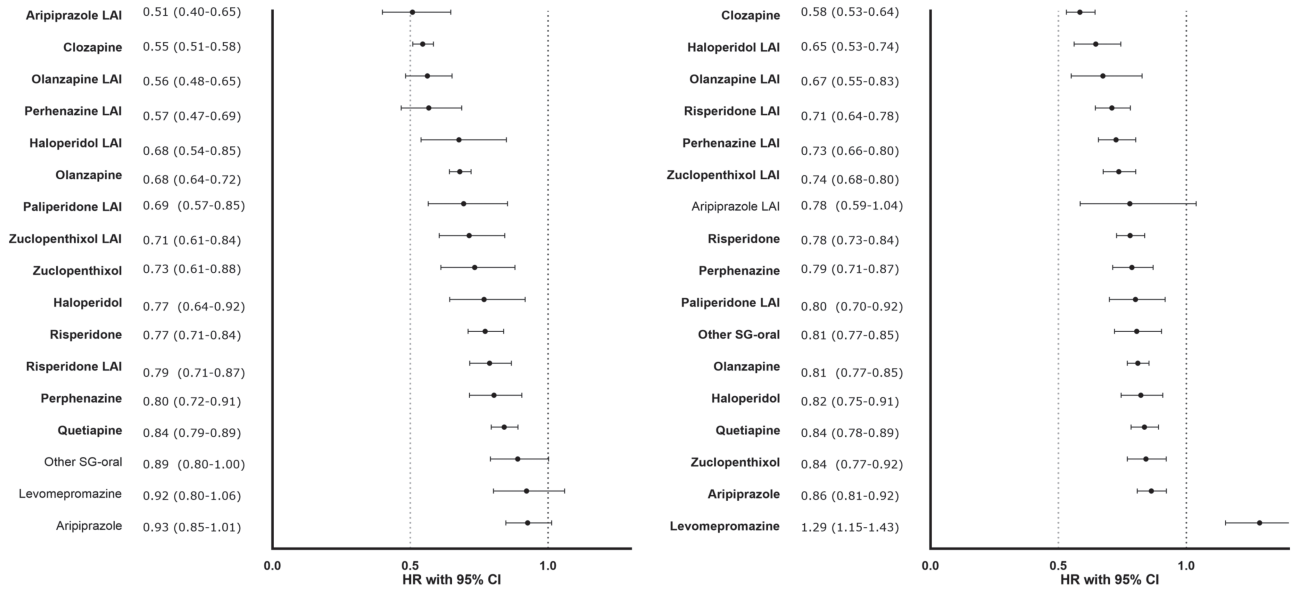

Fig. 2. Relative hazard of treatment failure (hazard ratio [HR], with 95% confidence interval [CI]) associated with specific antipsychotics in schizoaffective disorder (SCHAFF) compared with no use of antipsychotics, within-individual comparisons. In bold are depicted agents that are significant after Benjamini-Hochberg correction for 5% false discovery rate. Treatment failure consists of psychiatric hospitalizations, any changes in antipsychotic medication (switch, addition, discontinuation), and death due to any cause.

hospitalization when compared with antipsychotic only use ($P < .0001$). When compared with the most common antipsychotic monotherapies, combining mood stabilizer was beneficial for clozapine (HR 0.73, 0.62–0.86), olanzapine (HR 0.83, CI 0.71–0.98), quetiapine (HR 0.71, 0.61–0.84) and SG-LAI (HR 0.69, 0.52–0.91) in the Finnish cohort (figure 3). The results in the Swedish cohort were mainly in line with the Finnish results, but CIs were wider and the results more often nonsignificant.

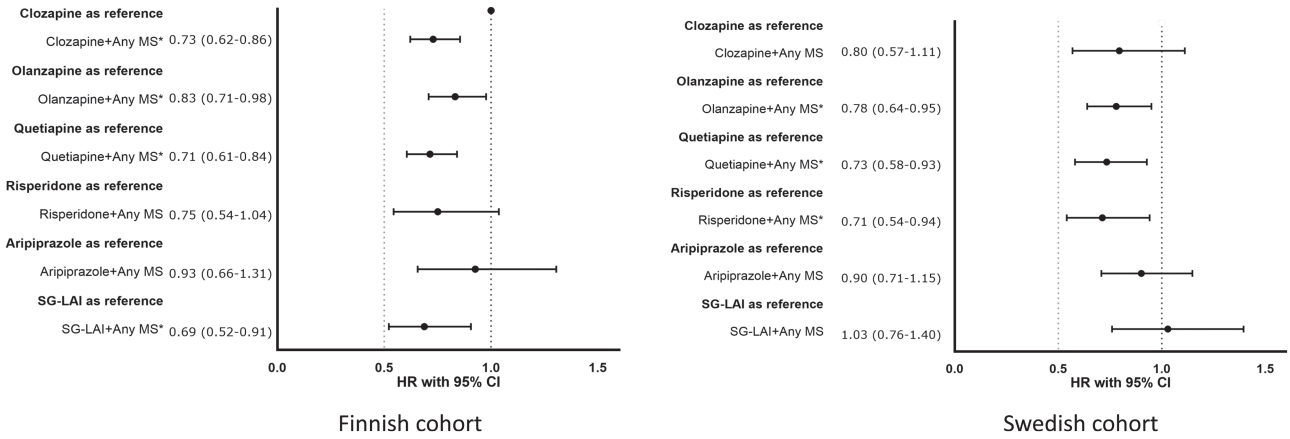

Fig. 3. Relative hazard of psychosis hospitalization (hazard ratio [HR], with 95% confidence interval [CI]) associated with combinations of specific antipsychotics and any mood stabilizer (MS) compared with specific antipsychotic monotherapies, within-individual comparisons. The agents that are significant after Benjamini-Hochberg correction for 5% false discovery rate are indicated with an asterisk (*).

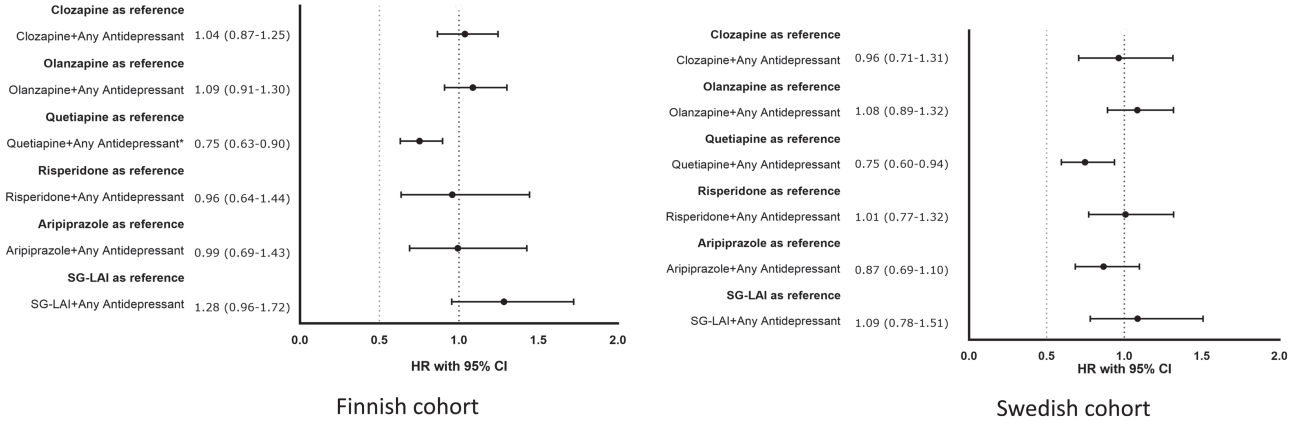

Fig. 4. Relative hazard of psychosis hospitalization (hazard ratio [HR], with 95% confidence interval [CI]) associated with combinations of specific antipsychotics and antidepressants compared with specific antipsychotic monotherapies, within-individual comparisons. The agents that are significant after Benjamini-Hochberg correction for 5% false discovery rate are indicated with an asterisk (*).

Antidepressant use was associated with a 10% decreased risk of psychosis hospitalization (HR 0.90, 0.83–0.97) in the Swedish cohort, but not in the Finnish cohort (1.00, 0.94–1.07). Of the specific commonly used antipsychotics, only quetiapine combined with an antidepressant was associated with a decreased risk in both cohorts compared with specific antipsychotic monotherapies (HR 0.75, 0.60–0.94 in the Swedish cohort, HR 0.75, 0.63–0.90 in the Finnish cohort) (figure 4).

BZDR use was associated with a 7% (HR 1.07, 1.01–1.14, Finnish cohort) and 21% (1.21, 1.13–1.30, Swedish cohort) increased risk of psychosis hospitalization. The results did not change when the first 30 days of use were censored from the analyses (HR 1.07, 1.01–1.15 in the Finnish cohort and HR 1.21, 1.12–1.30 in the Swedish cohort). Regarding the most common antipsychotics used, SG-LAI (HR 1.59, 1.22–2.09) and clozapine (HR 1.19, 1.01–1.41) combined with BZDRs were associated with a higher risk of psychosis hospitalization in the Finnish cohort when compared with specific antipsychotics without concomitant BZDRs (figure 5). For the Swedish cohort, no specific antipsychotic and BZDR combination was associated with an altered risk.

The results remained similar when the outcome was defined as any psychiatric hospitalization and not just hospitalization due to psychosis (supplementary table 4). The results remained similar for adjunctive pharmacotherapies: combining mood stabilizers with antipsychotics was associated with a decreased risk (HR 0.90, 0.85–0.95 in the Finnish cohort and HR 0.78, 0.72–0.86 in the Swedish cohort), combining antidepressants had varying results (HR 1.03, 0.97–1.09 in the Finnish cohort and HR 0.91, 0.83–1.00 in the Swedish cohort) and use of BZDRs was associated with an increased risk (HR 1.15, 1.09–1.21 in the Finnish cohort and HR 1.21, 1.11–1.32 in the Swedish cohort).

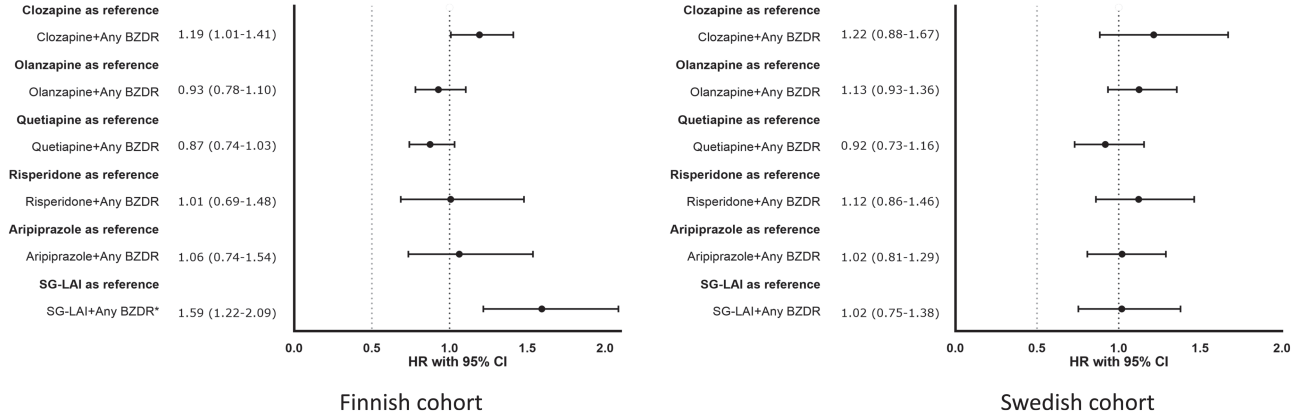

Fig. 5. Relative hazard of psychosis hospitalization (hazard ratio [HR], with 95% confidence interval [CI]) associated with combinations of specific antipsychotics and benzodiazepines and related drugs (BZDR) compared with specific antipsychotic monotherapies, within-individual comparisons. The agents that are significant after Benjamini-Hochberg correction for 5% false discovery rate are indicated with an asterisk (*).

Discussion

It is of great clinical importance to study purely SCHAFF patients, as a plethora of treatment modalities are used in clinical practice, although only paliperidone has an approved treatment indication for SCHAFF from EMA and FDA, and use of other treatments would be considered off-label use. As might be expected, exposure to antipsychotics, in general, was associated with a decreased risk of psychosis hospitalization. Concerning specific antipsychotics, exposure to LAIs or clozapine was associated with a lower risk than FG- and SG-oral pharmacotherapies in both nationwide cohorts. In addition, especially in the Swedish cohort, antipsychotic polytherapy was associated with a notable decrease in the risk of psychosis hospitalization. Of specific antipsychotics, use of levomepromazine or aripiprazole LAI was associated with a decreased risk of psychosis hospitalization in the Finnish cohort, but not in the Swedish cohort. For aripiprazole LAI, this could be due to the low number of users and as such, this result should be interpreted with caution. The risk of treatment failure (psychiatric hospitalization, any change in medication, death) was increased in the Swedish cohort during levomepromazine use, but it had no effect on the risk of treatment failure in the Finnish cohort. This could be due to levomepromazine's poor antipsychotic effect[20] and the possibly increased risk of mortality during levomepromazine use.[21]

The combination of antipsychotics and adjunctive mood stabilizers was associated with a lower risk of psychosis hospitalization in both cohorts as compared with antipsychotic monotherapy, which is important to note, as combining medications from two different groups can increase the risks associated with the treatments[22] and reduce adherence, and should thus not be undertaken without evidence on effectiveness.

The superiority of LAIs and clozapine is in line with previous studies that compared different antipsychotic treatments in large cohorts combining both schizophrenia and SCHAFF patients.[16,17,23] The superior effectiveness of LAIs[24,25] and clozapine[26] for schizophrenia has also been observed in meta-analyses. The effectiveness of these drugs is, at least to some extent, likely associated with better treatment adherence. This is in line with our observation on the risk of treatment failure; the risk associated with LAIs and clozapine was lower as compared with oral pharmacotherapies. Nonadherence to antipsychotic medications has been estimated to be between 41% and 50%.[27] However, adherence to LAIs[28] and clozapine[29] has been shown to be better than adherence to other antipsychotics, which could be due to regular appointments with healthcare professionals for administering antipsychotic injections and obligatory blood monitoring during clozapine use. Therefore, possible exacerbations of SCHAFF are likely more rapidly noticed and outpatient interventions are undertaken to prevent inpatient psychiatric hospitalization. However, our results show some differences between the effectiveness of different LAIs, and therefore, the superiority of LAIs may not be explained solely by better adherence and more frequent outpatient healthcare visits. In addition to clozapine's effectiveness on treatment-refractory psychotic symptoms, exposure to clozapine has been associated with a decreased risk of suicidal behavior and substance abuse, and it has been suggested to be especially effective on affective symptoms.[30,31] All of these factors relate to better treatment outcomes in SCHAFF.

Since SCHAFF symptomatology includes both schizophrenic and affective symptoms, adjunctive mood stabilizer or antidepressant use is common, even though the evidence-based effectiveness of this practice is inconclusive.[9–11] It has been proposed that the optimal treatment for the different subtypes of SCHAFF might be different; for the manic/bipolar subtype use of mood stabilizers could be useful, whereas the depressive

subtype could benefit from antidepressants.[3] Previous studies on the efficacy of adjunctive use of mood stabilizers in SCHAFF have been small and they have focused on specific combinations of antipsychotics and mood stabilizers.[32–35] Indeed, preceding information on the use of mood stabilizers as adjunctive therapy in SCHAFF has been scarce and due to limitations, very few conclusions could have been drawn. Our results suggest that add-on mood stabilizer use could be beneficial in SCHAFF. However, our study did not separate the different subtypes of SCHAFF, which could have yielded more clinically relevant information.

Evidence on adding antidepressants to schizophrenia/SCHAFF pharmacotherapy is also limited.[36] Our results differed between the two cohorts, as in the Swedish cohort exposure to antidepressants was associated with a decreased risk of psychosis hospitalization, whereas in the Finnish cohort this association was not observed. These differences could be due to different treatment guidelines and clinical practices between Finland and Sweden. It is also worth noticing that using BZDRs with antipsychotics was associated with an increased risk of psychosis hospitalization in both cohorts. This is especially important, as BZDRs were very widely used in both of our study cohorts. It is concerning that BZDRs were more commonly used than other adjunctive medications, even though the results suggest beneficial effects of mood stabilizers and antidepressants.

The strengths of this observational study include two large nationwide cohorts with thousands of patients and multiple years of follow-up time. Selection bias is minimal, since our study included all patients with SCHAFF in the nationwide registers (excluding a small number of patients who have only been treated in outpatient care in Finland). Therefore, our results represent a real-life setting and are generalizable to high-income countries that provide medications for free or with very low copayment for patients with serious mental disorders. Drug use was modeled with the PRE2DUP method[18] which has been shown to produce highly reliable estimates of drug use.[37] The within-individual model used in this study controls for all time-invariant covariates in the design, and the analyses were adjusted for multiple time-varying covariates, minimizing the common sources of bias in observational studies. The limitations of our study are related to the nature of the data in the nationwide registers, which were not originally designed for analysis methods such as the ones employed here. Register-based data lack information on many clinically important factors, such as the severity of the symptoms during specific drug exposures and thus, residual confounding may exist. We were not able to confirm the certainty of the diagnostics between SCHAFF and schizophrenia from the medical records since our study is register-based. However, SCHAFF- and schizophrenia diagnoses are carefully considered before the diagnosis is given, and in both Finland and Sweden diagnostics should always follow the ICD criteria. Patients with diagnostic uncertainties (change of diagnosis from SCHAFF to schizophrenia) were removed from the sensitivity analyses. One weakness of the current study was that we did not make a division according to the subtypes of SCHAFF, as the different subtypes or polarities of episodes (manic, depressive, or mixed) may respond differently to pharmacological treatments. This topic remains for future studies to elucidate upon. Psychological interventions are important when treating psychiatric disorders, but unfortunately, our data did not allow us to adjust our models for them. It is also noteworthy that both Finland and Sweden use the ICD-system, and therefore, these results may not be directly translatable to healthcare systems using DSM criteria.

In conclusion, our study found that use of antipsychotics, especially clozapine and LAIs, was associated with a decreased risk of psychosis hospitalization among individuals with SCHAFF in two nationwide cohorts. These results are in line with previous nationwide cohort studies, which combined both schizophrenia and SCHAFF patients. Add-on mood stabilizer treatment was associated with a significant decrease in the risk of psychosis hospitalization as compared with antipsychotic monotherapy in both cohorts, whereas use of antidepressants had varying results. Use of benzodiazepines with antipsychotics was associated with an increased risk of psychosis hospitalization. SCHAFF is a common, yet controversial, diagnosis in clinical psychiatry, and there is a gap between research-based knowledge and clinical practices on its pharmacotherapy. Therefore, more studies including only patients with SCHAFF are needed to determine the optimal pharmacotherapy for this disorder. Especially studies on adjunctive treatments should be performed, and the subtypes of SCHAFF should be separated, since the treatment response could differ among different types of SCHAFF patients or between episodes of different polarities.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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