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Five-Year Cumulative Exposure to Antipsychotic Medication After First-Episode Psychosis and its Association With 19-Year Outcomes

Tomi Bergström*[,1,2], Jyri J. Taskila[1], Birgitta Alakare[1], Päivi Köngäs-Saviaro[1], Jouko Miettunen[3,4], and Jaakko Seikkula[2]

[1]Department of Psychiatry, Länsi-Pohja Hospital District, Kemi, Finland; [2]Department of Psychology, University of Jyväskylä, Jyväskylä, Finland; [3]Center for Life Course Health Research, University of Oulu, Oulu, Finland; [4]Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

*To whom correspondence should be addressed; Kauppakatu 5 a, 94100 Kemi, Finland; tel: +358400986486, e-mail: tomi.bergstrom@lpshp.fi

Background: **The long-term effectiveness of antipsychotic maintenance treatment after first-episode psychosis (FEP) is contested. In this real-world observational study, we examined how cumulative exposure to antipsychotics within the first 5 years from FEP was associated with the 19-year outcome.** ***Methods:*** **Finnish national registers were used to detect all patients who were hospitalized due to non-affective psychosis in the mid-1990s, and who were treatment naïve prior to the inclusion period (*N* = 1318). Generalized linear models with logit link function were used to estimate how cumulative exposure to antipsychotics within the first 5 years from onset was associated with mortality, work capability, and the use of psychiatric services at the end of the 19-year follow-up. To adjust for confounding by indication, the primary outcome analyses implemented stabilized inverse probability of treatment weighting using propensity scores.** ***Results:*** **Persons with a higher cumulative exposure to antipsychotics within the first 5 years from FEP were more likely to still be receiving antipsychotics (adjusted odds ratio [OR] = 2.1; 95% CI: 1.5−2.8), psychiatric treatment (OR = 1.4; 95% CI: 1.1−1.7), and disability allowances (OR = 1.3; 95% CI: 1.01−1.6) at the end of the 19-year follow-up, as compared to low/zero-exposure. Higher cumulative exposure was also associated with higher mortality (OR = 1.5; 95% CI: 1.1–2.1).** ***Conclusions:*** **After adjustment for confounders, moderate and high cumulative exposure to antipsychotics within the first 5 years from FEP was consistently associated with a higher risk of adverse outcomes during the 19-year follow-up, as compared to low or zero exposure. Due to potential unmeasured confounding, controlled trials are needed.**

Key words: cohort study/long-term follow-up/mortality/schizophrenia/work capability

Introduction

Antipsychotic medication can reduce the intensity of acute psychotic symptoms among people diagnosed with schizophrenia-spectrum disorders.[1] Many official treatment guidelines also recommend that antipsychotic treatment should be continued for several years following an acute psychotic episode, since a maintenance treatment strategy has been associated with a lower incidence of relapses and with a decrease in rehospitalization rates.[2–4] However, the risk-benefit ratio of longer-term maintenance treatment with antipsychotics is unclear, and current knowledge comes mainly from observational studies.[3] Some of these studies have indicated that the efficiency of antipsychotics in preventing relapse might actually decrease over time,[5–7] leading eventually to a poorer functional outcome[8] as well as an increased risk of premature mortality,[9] potentially due to a range of side effects following prolonged dopamine D2 blockade.[8,10]

In line with the above, a number of studies have indicated that a more individualized need-adapted response to psychosis—involving a lesser exposure to antipsychotics after acute psychosis—could, in some cases, be associated with a more favorable long-term outcome.[11] Recent studies have also demonstrated that if intensive psychosocial support is guaranteed, antipsychotics may not be immediately required in all cases of first-episode psychosis (FEP),[12,13] and that there exists a subgroup of patients who might benefit from systematic antipsychotic

dose reduction.[2,8] For example, in one trial, Wunderink et al[14] found that dose reduction/discontinuation of antipsychotics after acute psychosis showed superior long-term recovery and (in particular) better functional outcome rates as compared to maintenance treatment.

Nevertheless, evidence concerning more individualized treatment strategies is still scarce, and many methodological issues have to be taken into account. For example, Correll et al[3] noted that in longer-term studies, there is always a greater chance of bias, and—especially in uncontrolled studies—persons with more severe and impairing symptoms are more likely to receive antipsychotics. In long-term nationwide register studies, a higher cumulative exposure to antipsychotics,[15–17] and especially treatment with long-acting injections and clozapine, has been associated with significantly less treatment failure[18] and lower mortality,[16] as compared to persons not treated with antipsychotics. However, the design of register studies has been criticized due to potential uncontrollable confounders; these could be associated with how certain medications were used,[19] and with systematic differences in illness duration across treatment groups.[20] In addition, most previous studies have included only patients with a schizophrenia diagnosis, raising the possibility that there could have been unobservable antipsychotic treatment periods prior to the diagnosis and the initiation of the follow-up.

Given that nationwide register-based studies contradict most other studies on longer-term follow-up concerning antipsychotic exposure and treatment outcomes,[3] and given that this contradiction might be due to systematic sampling bias and uncontrollable confounders relating to study design,[19,20] there is a clear need to evaluate how antipsychotic medication is associated with long-term outcomes in a nationwide register-based sample of first-episode patients who were (1) treatment naïve prior to the onset of psychosis, and among whom (2) the potential exposure and follow-up time remained approximately the same. There is also a lack of functional long-term outcome data: previous studies have focused mainly on rehospitalization rates and on changes in observable symptoms within a certain time frame, and these aspects are not necessarily causally associated with longer-term social functioning and wellbeing.[8] To address these issues, the present study examined how, in a register-based sample, cumulative exposure to antipsychotics within the first 5 years from FEP was associated with 19-year outcomes, including work capability, the use of mental health services, and premature mortality.

Methods

Design

Data for this register-based cohort study were derived from Finnish national registers as part of a research project which aimed to evaluate the long-term outcomes of a range of treatment approaches in a naturalistic setting.[12] For this sub-study, supplementary authorizations were granted by the *Finnish Institute for Health and Welfare* (THL), the *Social Insurance Institution* (SII), and *Statistics Finland* (SF).

In order to minimize the survival and other time-related biases associated with register-based studies,[19,20] care was taken to ensure (1) that the potential exposure time to antipsychotics and the overall follow-up time remained approximately the same for the entire cohort, and (2) that the follow-up time was long enough for a range of outcomes to occur. Thus, in forming the sample, the first goal was to detect from Finnish healthcare service records all those FEP patients whose first contact with mental health services due to non-affective psychosis occurred 19 years previously (figure 1).

As there are limitations in Finnish national registers regarding medical information prior to the year 1995, and data collection was conducted during the years 2015 and 2017, consistent 19-year follow-up was possible only for the inclusion years 1995 and 1996. Based on this, the *Finnish Care Register of Health Care* (CRHC) (formerly *Hospital Discharge Register*) provided by THL, was used to detect all people who had one or more entries with non-affective psychosis (ICD-9 codes = 295–295.9 and 297–298.9; ICD-10 codes = F20−29.1) between January 1, 1995 and December 31, 1996 (N = 10 859).

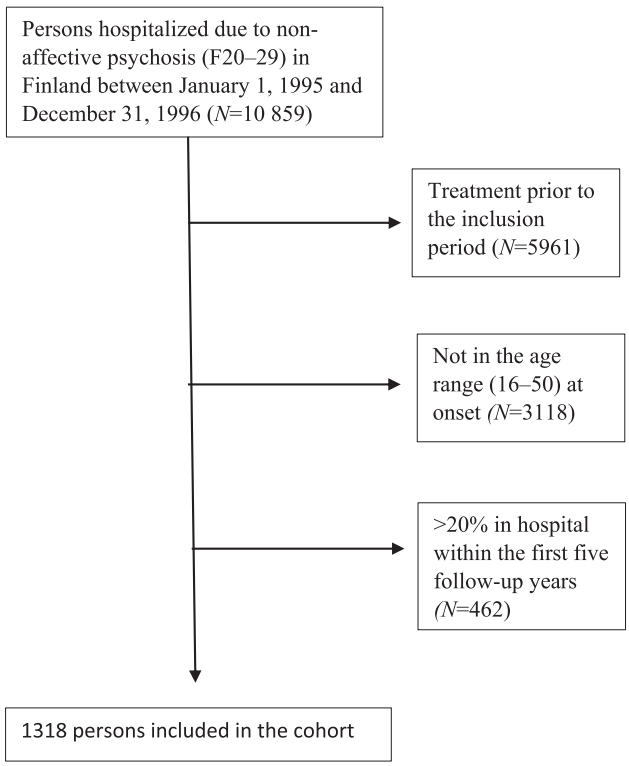

Fig. 1. Flow of inclusion and exclusion within the research cohort.

Due to a lack of reliable information on outpatient treatment prior to 2011, only persons with one or more hospital admissions were included. In order to further increase the uniformity of the cohort, only people aged 16–50 at onset were included, with exclusion of all individuals who had received psychiatric specialized healthcare, or medical treatment, or disability allowances for mental health disorder prior to the inclusion period. Overall, 1780 people fulfilled the inclusion criteria. In order to increase comparability with earlier register-based studies[17,18] as well as the validity of the antipsychotic exposure estimation, 462 individuals were further excluded, as they had spent over 20% of the first 5 years from onset in hospital; this might bias the estimated exposure to antipsychotics based on medication purchases during outpatient care[17] (for more details see covariates and predictors).

National registers provided information regarding demographics, the use of mental health services, medical treatment, mortality, and disability allowances from onset to the end of the follow-up. Data from one catchment area ($N = 17$) had been collected separately as part of an earlier research project.[21] For each cohort member, the follow-up time was set to start from the first register entry and to end at either death or 6936 days (19 years) after the first entry.

Covariates and Predictors

Comorbid somatic illnesses at the baseline were evaluated by grouping patients via the Anatomical Therapeutic Chemicals (ATC) classification, based on first-year medication purchases. From CRHC, we obtained data on gender, age at onset, Global Assessment Scale (GAS) scores (0 = severe impairment, 100 = superior functioning at the onset of first hospital admission), and diagnosis. The diagnoses had been set as a standard procedure by physicians in their everyday practice. Prior to 1996, the diagnoses were set on the basis of the ICD-9 criteria; thereafter, ICD-10 was applied. The distinction between schizophrenia (F20) and other non-affective psychoses (F21−29) was used as one of the covariates since persons with a schizophrenia diagnosis could be expected overall to demonstrate more severe and prolonged symptomatology[22]—and thus a higher risk of different outcomes, and also a higher cumulative exposure to antipsychotics—than persons with other non-affective psychosis diagnoses. Within our analyses we grouped patients according to whether or not they had at least one register entry with schizophrenia within the first 5 years from onset.

We obtained information on antipsychotic medication from the register of reimbursed medication provided by SII. The data covered all purchased antipsychotics (N05A; excluding lithium) from start of the follow-up (onset of FEP) to the end of the follow-up. Cumulative exposure to medication in the first follow-up years was estimated using the *defined daily dose* (DDD), in a similar manner to previous studies that have used national register samples.[15,17] Thus, initially, the sum of the dispensed medication was calculated in terms of the DDD. Next, the sum was divided by the number of follow-up days minus the number of hospital days, bearing in mind that the national registers do not provide valid information on the medication used during hospital treatment. Because the length of time spent in hospital might have biased the exposure estimation, the analyses were performed on the group that spent less than 20% of their first 5 follow-up years in hospital. Here we also followed the same procedure as in earlier studies.[17]

The aim was to evaluate how cumulative exposure during the first follow-up years predicted later outcomes. Because there is a general lack of information concerning the exposure to antipsychotics after the first 3 years from acute psychosis, and because the length of the follow-up time increases the risk of biases,[3] the measurement point was set at 5 years from first onset; thus the exposure estimates were calculated on the basis of *all medication purchases that took place prior to 1825 days (5 years) from onset*. Furthermore, because the association between the cumulative 5-year exposure and the 19-year outcomes was likely to be biased due to deaths within the first onset years, all persons who died prior to the 5-year measurement point were treated as missing information in the primary outcome analysis (for details see statistical analysis). In order to estimate how the potential survival bias affected the primary outcomes, separate analyses were conducted to study the usage of antipsychotics by those who had died within the first 5 follow-up years (supplementary table 1).

In the final phase, all the patients were categorized into 4 DDD groups using the same cutoff points that were applied in previous register-based cohort studies.[15,17] Hence, the groups were defined as (1) *zero medication*, (2) *small or occasional exposure* (DDD < 0.5/day), (3) *moderate exposure* (0.5–1.5 DDD/day), and (4) *high exposure* (>1.5 DDD/day). Within the first 5 years from onset, 4% did not receive any antipsychotics, while 70% had low cumulative exposure, 22% moderate exposure, and 4% high cumulative exposure.

The highest and lowest exposure groups were significantly smaller than the other groups. Hence, for further analyses the cumulative exposure to antipsychotics was dummy coded to 1 = *moderate/high exposure,* and 0 = *low/zero-exposure* within the first 5 years from onset. Because earlier studies[16,18] have indicated that, as compared to zero exposure to antipsychotics, the use of any antipsychotics—and especially the use of clozapine and injectable antipsychotics—is associated with a lower risk of adverse

events, *usage vs zero-use* of these medicines was compared in additional analyses (supplementary tables 2–4).

Outcome Variables

Four primary outcome variables were formed by combining information from different register sources:

1. Death (including cause of death);
2. Treatment contact at the end of the follow-up: *yes* = if there were one or more hospital admissions and/or outpatient visits after 6570 days from onset (ie, during the last follow-up year);
3. Antipsychotic medication at the end of the follow-up: *yes* = if there was one or more purchased antipsychotics and/or antipsychotics during hospital treatment after 6570 days from onset;
4. Disability allowance at the end of the follow-up: *yes* = if, after 6570 days from onset, one or more days were spent on a full-time or partial disability allowance granted due to decreased work capability caused by a mental health disorder.

Statistical Methods

Chi-square and U-test were first used to compare group differences between moderate/high- and low/zero-exposure groups. As the results showed statistically significant differences in the baseline characteristics of the 2 exposure groups (table 1), we applied stabilized inverse probability of treatment weighting (SIPTW)[23,24] to adjust for potential confounding by indication.

As a first step, the propensity scores for each individual were calculated via multivariate logistic regression to predict how cumulative exposure to antipsychotics was influenced by potential confounders. These included the available characteristics at onset, ie, the demographic data (age and gender), plus the clinical data, consisting of GAF scores, comorbid somatic conditions (ATC groups), and the diagnosis. For the analysis of cumulative exposure and the clinical outcome at the end of the follow-up, the propensity scores were further adjusted for the loss caused by deaths during the entire 19-year follow-up. Correspondingly, for the analysis of antipsychotic exposure and deaths after a 5-year cumulative exposure, the propensity scores were adjusted for loss caused by deaths within the first 5 follow-up years. The potential survival bias was explored via additional analyses comparing the demographical and clinical characteristics of those who died within the first 5 follow-up years with those who survived (supplementary table 1).

After calculation of propensity scores for the different analyses, the scores were used to calculate the SIPTWs for each individual. Thus, the calculated weights were P_i/PS

Table 1. Group Characteristics and Differences in Cumulative Exposure to Antipsychotics Within the First 5 Years From FEP

	Sample Without Weighting			Inverse Probability of Treatment Weighted Sample		
	Low/Zero Exposure (N = 966)	Moderate/High Cumulative Exposure (N = 352)	P	Low/Zero Exposure (N = 964)	Moderate/ High Exposure (N = 354)	P
Baseline						
Gender, male	51%	68%	.000	55%	55%	.967
Age (mean/SD)	32/8	30/8	.000	31/8	31/8	.619
Schizophrenia	35%	72%	.000	44%	44%	.952
GAS (mean/SD)	35/11	35/12	.994	35/11	35/11	.983
Comorbidity						
Metabolism[a]	0.5%	0.9%	.489	0.6%	0.6%	.908
Cardiovascular[b]	11%	10%	.527	10%	10%	.726
Respiratory[c]	33%	27%	.024	31%	30%	.449
Outcomes						
Treatment contact[d]	45%	56%	.001	46%	54%	.013
Antipsychotics[d]	66%	78%	.000	65%	80%	.000
Disability allowance[d]	54%	65%	.000	55%	61%	.047
Death (all-cause)[e]	11%	15%	.059	11%	16%	.015
Suicide[e]	2%	5%	.007	2%	4%	.039
Natural cause[e]	6%	7%	.645	6%	9%	.104

Note: ATC, Anatomical Therapeutic Chemicals; GAS, Global Assessment Scale.
[a]If one or more medications purchased with ATC-code A at first year from onset.
[b]If one or more medications purchased with ATC-code C at first year from onset.
[c]If one or more medications purchased with ATC-code R at first year from onset.
[d]At the end of the 19-year follow-up.
[e]Death after 5 years from onset.

for those with moderate/high cumulative exposure, and $(1\text{-}P_t)/(1\text{-}PS)$ for those with low/zero exposure, where P_t is the proportion of individuals in the treatment (moderate/high exposure to antipsychotics) group and PS the propensity scores. As a final phase, weighted generalized linear models with binomial probability distribution and a logit link function were used to predict primary long-term outcomes following the cumulative 5-year antipsychotic exposure.

Additional analyses were conducted separately for schizophrenia and other psychosis groups (supplementary tables 5 and 6) to ascertain whether the conclusions from the main analysis remained valid. To further assess the robustness of the association between cumulative antipsychotic exposure and long-term outcomes, sensitivity analyses with E-values[25,26] were conducted for each primary outcome to examine the extent to which unmeasured confounders rendered significant ratio measures above 1.0 to be nonsignificant.

Results

Sample Characteristics

The mean age at onset was 31.1 years (SD 8), and 55% of the cohort were males. We found that 45% of the cohort members had one or more entries with a schizophrenia diagnosis during their first 5 follow-up years. Persons with a higher cumulative exposure to antipsychotics within the first 5 years from onset were more often males and more often diagnosed with schizophrenia. In addition, more of these persons were still in treatment contact, on a disability allowance, and on antipsychotic medication at the end of the follow-up, as compared to those with low/zero-exposure (table 1). Conversely, the use of mental health services at the end of the follow-up was significantly lower for those who did not receive any antipsychotic medication during their first 5 years from onset (supplementary table 1).

In the subgroup analyses, zero exposure to antipsychotics was not statistically significantly associated with the overall mortality rate, including suicides, prior to or after the first 5 years from onset (supplementary tables 1 and 2). Persons who had received injectable antipsychotics (supplementary table 3) and/or clozapine (supplementary table 4) were more likely to still be in treatment contact and on disability allowance at the end of the follow-up. The use of injectable antipsychotics and/or clozapine during the first 5 years was associated with a lower mortality during the first 5 years from onset (supplementary table 1), but not thereafter (supplementary tables 3 and 4); moreover, after adjustment for confounders, there were no indications that the use of injectable antipsychotics and/or clozapine would have decreased the overall mortality ratio in the 19-year follow-up. In fact, there were more deaths due to natural causes in the groups that received injectable antipsychotics and/or clozapine, but the difference did not reach statistical significance (supplementary tables 3 and 4).

No significant differences at onset regarding demographic and clinical characteristics were observed after SIPT weighting, which would indicate that the procedure effectively removed confounding. Furthermore, there were indications that the cumulative antipsychotic exposure possessed independent explanatory power in relation to the primary outcome variables, given that the above-mentioned outcomes remained constant after the SIPT weighting (table 1).

Primary Outcomes

After adjustment for confounding by indication via SIPTW, it was found that high/medium cumulative exposure to antipsychotic medication within the first 5 years from first-onset psychosis was statistically significantly associated with ongoing treatment contact, antipsychotic medication, and disability allowances at the end of the follow-up, as compared to persons with low/zero exposure to antipsychotics (table 2). Persons with higher cumulative antipsychotic exposure were also more likely to die after the first 5 years from onset, especially due to suicide (table 2). Higher cumulative exposure also demonstrated an increased risk of death from natural causes, but this association was not statistically

Table 2. Associations Between Moderate/High 5-Year Cumulative Exposure to Antipsychotics and Outcomes at the End of the 19-Year Follow-up, as Compared to the Low/Zero Antipsychotic Exposure Group

	OR[a]	95% CI	*P*	E-value	
				For effect estimate[b]	For CI Limit[c]
Treatment contact	1.4	1.1–1.7	.01	1.6	1.3
Disability allowance	1.3	1.01–1.6	.04	1.5	1.1
Antipsychotics	2.1	1.5–2.8	<.001	2.3	1.7
Death (all-cause)[d]	1.5	1.1–2.1	.02	2.4	1.4
Suicide[d]	2	1.1–3.9	.04	3.4	1.4
Death from natural causes[d]	1.4	0.9–2.2	.1	2.1	1

Note: [a]The analyses implemented inverse probability of treatment weighting using the propensity scores.
[b]The minimum strength of association on the risk ratio scale that an unmeasured confounder would need to possess on both the exposure and the outcome in order to fully explain away the observed association.
[c]E-values for the 95% CI limit closest to the null denote the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to possess on both the exposure and the outcome in order to shift the 95% CI to include the null value.
[d]After the first 5 years from onset.

significant (table 2). The findings remained constant after subgroup analyses, including only persons with vs without a schizophrenia diagnosis (supplementary tables 5 and 6). However, it should be noted that in the subgroup analyses, the results did not reach statistical significance, potentially due to the notable decrease in sample size.

E-value estimators for most of the outcomes can be regarded as moderately robust. This gave further confirmation that cumulative exposure to antipsychotics exhibited explanatory power that was at least partially independent of the unmeasured confounders. It is nevertheless possible that a moderate confounder association could move the confidence interval to include 1. This seems to be especially the case with the observed association between cumulative antipsychotic exposure and disability allowances at the end of the follow-up, since—according to the calculated E-values—even a weak unmeasured confounder could explain away the observed association (table 2).

Discussion

This study aimed to examine how cumulative exposure to antipsychotics within the first years from FEP was associated with different outcomes at the 19-year follow-up. According to the main findings, persons who demonstrated a higher exposure to antipsychotic medication within the first 5 follow-up years were more likely to be still receiving mental health treatment and a disability allowance for mental health disorders almost 2 decades subsequent to FEP. After adjustment for confounders, a higher cumulative antipsychotic exposure during the first 5 years from onset was also associated with an increased risk of premature mortality during the long-term follow-up.

The overall findings are in line with previous observational studies, in which long-term maintenance treatment—and thus a higher exposure to antipsychotics—was associated with adverse outcomes.[5–7,9] One possible explanation for this pattern is that the prolonged blockage of dopaminergic pathways can eventually harm mechanisms that are essential for long-term survival,[8,10] even if blockage of the dopaminergic pathways could simultaneously reduce distressing experiences and/or behavior within a certain time frame. However, it should be noted that we observed significant differences in baseline characteristics between the exposure groups, indicating the possibility of reverse-causation, with more symptomatic patients being likely to receive longer-term antipsychotic maintenance treatment. This confounding effect makes it challenging to draw firm conclusions on the long-term effectiveness of antipsychotics-based maintenance treatment via purely register-based information, despite systematic attempts to explore and control the observable confounding factors.

It is nevertheless notable that in the analyses conducted specifically on the schizophrenia group, we found no association between exposure to antipsychotics and a decreased risk of premature mortality or other adverse outcomes. Given that we used the same register sources and similar measurements as were used in earlier register-based studies,[15–17] it is likely that the contradiction with previous studies derives from our efforts to minimize the effect of disorder duration. In this respect, our findings support earlier critiques suggesting that there could have been uncontrollable statistical bias in earlier nationwide cohort studies, within which the aim was to include *all people with a schizophrenia diagnosis*, with a range of onset years.[19,20] It can be argued that in the latter procedure, persons who survived with medication to reach the follow-up were more likely to be included in the analysis than those who died prior to inclusion; moreover, persons whose onset occurred *during* the follow-up might not have had enough time to develop adverse outcomes. The inclusion of only people with a schizophrenia diagnosis carries with it the possibility that a certain severity level after FEP had already been exceeded, also involving the possibility of antipsychotic usage periods prior to diagnosis and follow-up. This would explain why in our study there were so few non-users as compared to previous cohort studies.[16]

In addition, our primary goal was not to focus on the current use of medication, but rather on the long-term outcomes after a predetermined observation period from first clinical onset. While it is possible that patients with a schizophrenia diagnosis who are not currently taking antipsychotics have an increased risk of adverse outcomes over a certain time frame, this might reflect the fact that people who do not comply with treatment are at a higher risk of death and relapses due to underlying health risks and behaviors.[19] This, together with withdrawal effects,[27] could explain why an ongoing use of antipsychotics (and thus a higher cumulative exposure to antipsychotics over a certain time frame) might appear to give protection from certain adverse outcomes—even if over a longer period of time, maintenance treatment following FEP would not, in fact, decrease the overall risk of adverse events, as demonstrated in this study. The factors operating here would also explain why the mortality gap between people with schizophrenia and the general population is widening,[28] and why the recovery rate has remained unsatisfactory in long-term follow-ups.[29,30]

Strengths and Limitations

The Finnish registers are considered to be a reliable source of information, even if they were not developed for the purpose of scientific research.[31] In the 1990s, the hospital discharge register alone did capture persons with diagnosable non-affective psychosis.[32] This aspect was also addressed in a previous study,[12] where it was found that

the crude annual incidence, and other clinical characteristics of non-affective FEP in the sample, were in line with studies that had previously included FEP patients in real-world settings.[33–35] On this basis, the external validity of the findings of the present study can be regarded as good.

Another strength was the continuous study design, with an exceptionally long follow-up time. This minimized the effect of disorder duration (and thus variation in potential treatment time) and other intervening variables by focusing on the cumulative exposure to antipsychotics within a predetermined timeframe, among persons who were treatment-naïve prior to inclusion. This decreased the risk of associations involving potential uncontrollable confounders that would affect both a particular outcome and the ongoing use of a particular medication. It simultaneously addressed the question of why some findings from earlier register-based studies seem paradoxical in relation to the known short- and long-term side effects of antipsychotics.[8]

Comprehensive sensitivity and subgroup analyses with stabilized inverse probability weighting were conducted to examine the effect of confounding by indication. Even though multiple comparisons increased the probability of chance findings, the results consistently indicated (1) that cumulative exposure to antipsychotics during the first 5 follow-up years had independent explanatory power, but also (2) that there could have been undetectable variables, and (3) that it is unlikely that the weighted population accounted for the totality of the group differences, due to the general limitations of the data. Note that because the information was gathered as part of a larger research project with a different primary goal, there was a lack of information on a number of individual factors, potentially affecting how the antipsychotics were used in the first place. For example, it was possible to evaluate comorbid somatic illnesses only at a crude level, ie, on the basis of first-year medication purchases. This is because, at the time of onset, there was no information in the national registers concerning the outpatient treatment provided by either specialized or primary healthcare services.

It was noticeable that almost all the patients received antipsychotics within the first years from clinical onset, and also those with lower exposure during the first follow-up years demonstrated high mortality ratio, plus a prolonged use of medication and services. As there was no control group, it is not possible to draw a firm conclusion as to whether or not the antipsychotics themselves had caused these outcomes. Moreover, a lack of medical information on the actual usage of antipsychotics, especially during hospital treatment, further increased the risk of measurement errors; this was despite attempts to control for missing information in a manner similar to previous studies.[15,17] All in all, more controlled designs will be needed in the future to increase internal validity; these will also include more sophisticated analyses to evaluate the actual use of medication, given the general limitations regarding the use of DDDs for research purposes.[36]

Despite these limitations, the overall findings would appear to enable valid comparisons with previous register-based studies.[15–18] We used similar data sources and similar procedures, with the exception of the changes in the inclusion and follow-up parameters, which we applied in order to address some previous critiques.[19,20] It should be noted that due to our methodology, the sample size was significantly smaller than in previous register-based studies. Although the overall sample size should have adequate power for statistical analyses, this aspect could lead to chance findings in some subgroups

Conclusion

When compared with low/zero-exposure to antipsychotics, a higher cumulative exposure to antipsychotic medication during the first 5 years from FEP was consistently associated with adverse outcomes in the 19-year follow-up. However, due to potential uncontrollable confounding and to other limitations relating to the study design, very tentative conclusions can be suggested regarding the causality of the observed association.

The overall results suggest that register-based studies present a significant risk for different sources of bias; these relate especially to sampling and to other confounding issues, and they could also explain previous contradictory findings concerning long-term exposure to antipsychotics. All in all, there is an urgent need for controlled trials to evaluate the risk-benefit ratio of long-term maintenance treatment vs more individualized treatment strategies.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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