Poster P.3.d.015

# Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia

Jari Tiihonen[1,2], Ellenor Mittendorfer-Rutz[2], Kristina Alexanderson[2], Maila Majak[3], Juha Mehtälä[3], Fabian Hoti[3], Erik Jedenius[4], Dana Enkusson[4], Amy Leval[4], Jan Sermon[5], Antti Tanskanen[1,2,6], and Heidi Taipale[2,7]

[1] University of Eastern Finland, Department of Forensic Psychiatry, Niuvanniemi Hospital, Kuopio, Finland ; [2] Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden; [3] EPID Research Oy, Espoo, Finland; [4] Janssen Cilag, Solna, Sweden; [5] Janssen Cilag, Beerse, Belgium; [6] National Institute for Health and Welfare, The Impact Assessment Unit, Helsinki, Finland; and [7] University of Eastern Finland, School of Pharmacy, Kuopio, Finland

**Background:** Controversy remains as to whether antipsychotics increase or decrease the risk of death among patients with schizophrenia, and it is not known if there are any differences between long-acting injections (LAI) versus equivalent oral formulations in this regard. We aimed to study mortality in schizophrenia during specific antipsychotic treatments.

**Method:** We linked prospectively gathered nationwide register-based data during 2005–2013 to study all-cause mortality among all patients aged 16–64 years with a schizophrenia diagnosis in Sweden (N=29,823 in the total prevalent cohort; N=4,603 in the incident cohort of newly diagnosed patients). The effect of 20 clinical and sociodemographic co-variates was adjusted for in multivariate Cox regression. Sensitivity analyses with the incident cohort were conducted to control for survival bias. The main outcome was adjusted hazard ratio (aHR) for all-cause mortality.

**Results:** During the mean follow-up of 5.7 years, 2,515 patients (8.4%) died. During the maximum follow-up of 7.5 years, the lowest cumulative mortality was observed for second generation (SG) LAI use (7.5%). The corresponding proportions and aHRs compared to SG LAI use were 12.3% (aHR 1.37, 95% CI 1.01–1.86) for first generation (FG) LAIs, 8.5% (1.52, 1.13–2.05) for SG orals, 12.2% (1.83, 1.33–2.50) for FG orals, and 15.2% (3.39, 2.53–4.56) for no use of antipsychotics. Use of any antipsychotics was associated with substantially decreased risk of death when compared with no use of antipsychotics (unadjusted HR 0.60, 95% CI 0.55–0.66; aHR 0.44, 95% CI 0.39–0.49). Concerning specific agents, the lowest mortality was observed during use of paliperidone LAI (0.11, 0.03–0.43), oral aripiprazole (0.23, 0.15–0.34), and risperidone LAI (0.31, 0.23–0.43). In pairwise LAI-oral comparison, LAIs were associated with 33% lower mortality than equivalent orals (aHR 0.67, 95% CI 0.56–0.80). The results of the sensitivity analyses were consistent with the primary analyses. In the incident cohort, the number of deaths (n = 152 total) during specific antipsychotic treatments were too low for meaningful analysis for several specific agents when compared with no use of antipsychotic. The adjusted HRs were 0.15 (0.04–0.53) for SG LAIs, 0.53 (0.35–0.80) for SG orals, 0.64 (0.34–1.21) for FG LAIs, and 0.66 (0.34–1.29) for FG orals. Use of any antipsychotic was also associated with substantially lower risk of death (0.54, 0.36–0.80) when compared with no use.

Figure 1. Kaplan-Meier curve on risk of mortality in first (FG) and second (SG) generation oral and long-acting injection (LAI) use compared with no antipsychotic use. The patients contribute to several groups. 5685 of 29,823 (19%) of patients used antipsychotics throughout the entire follow-up time without gaps, and 24,138 (81%) of patients contributed both to antipsychotic use and non-use time. During maximum follow-up of 7.5 years, the lowest cumulative mortality rate was observed for SG LAI use (7.5%).

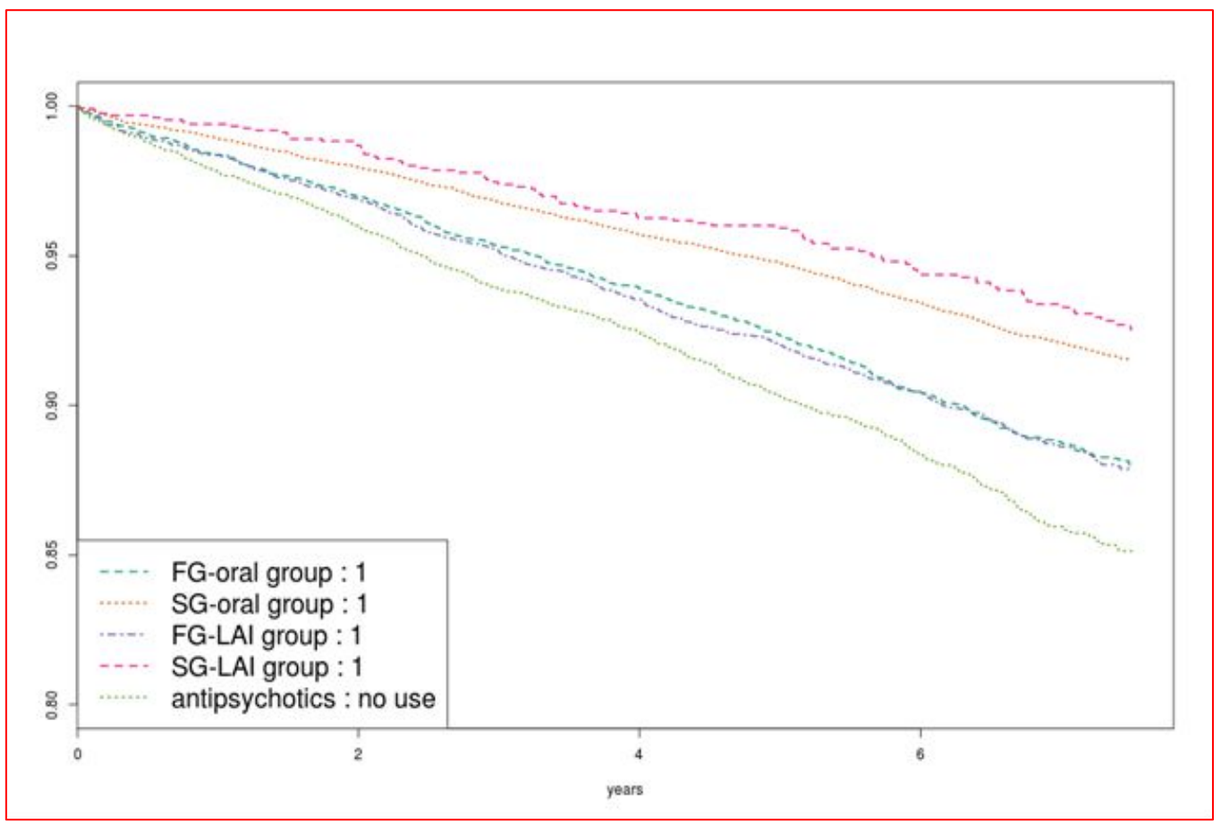
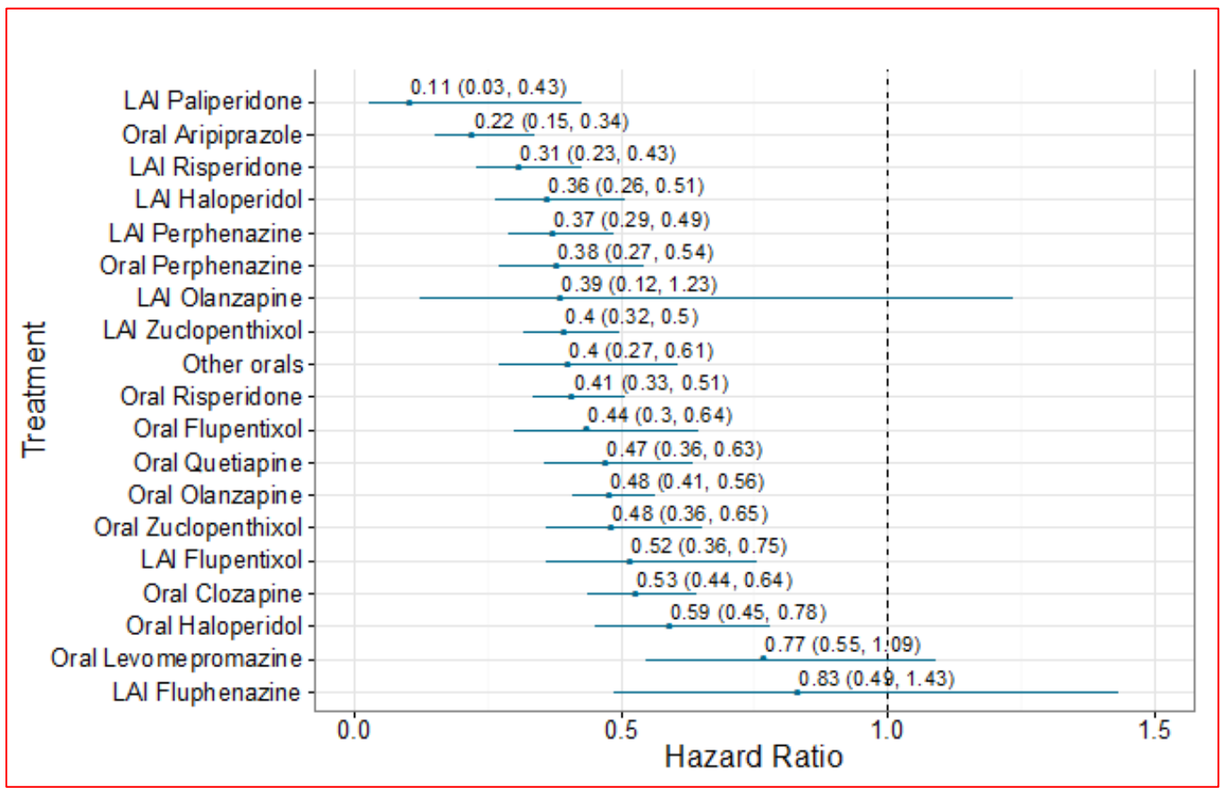



Figure 2. The adjusted Hazard Ratios of mortality during exposure to antipsychotic monotherapies compared with no use in the prevalent population (all LAIs and 10 most frequently used orals, all deaths included; no censoring of hospital deaths which were considered attributable to the last exposure period in outpatient care). All treatments except olanzapine LAI, levomepromazine and fluphenazine LAI survived Bonferroni correction (level of significance $p < 0.0025$).




**Conclusions:** Mortality among patients with schizophrenia is over 40% lower during those time periods, when patients use antipsychotics compared to when they do not. LAI use is associated with an approximately 30% lower risk of death compared with the equivalent oral agents. SG LAIs and oral aripiprazole are associated with the lowest mortality.

**Conflict of Interest Disclosures:** Jari Tiihonen reports serving as a consultant to the Finnish Medicines Agency Fimea, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-La Roche, Janssen-Cilag, Lundbeck, and Organon; receiving fees for giving expert testimonies to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Otsuka and Pfizer; receiving lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Novartis, Otsuka, Pfizer; receiving grants from Stanley Foundation and the Sigrid Jusélius Foundation; serving as a member of the advisory boards for AstraZeneca, Eli Lilly, Janssen-Cilag, and Otsuka, and participating in research projects funded by Janssen-Cilag and Eli Lilly with grants paid to Karolinska Institutet. Kristina Alexanderson has an unrestricted research grant from Biogen. Fabian Hoti, Maila Majak, and Juha Mehtälä reported being employed by EPID Research, which is a contract research organization that performs commissioned pharmacoepidemiological studies, and thus its employees have been and currently are working in collaboration with several pharmaceutical companies. Antti Tanskanen and Heidi Taipale reported participating in research projects funded by Janssen-Cilag and Eli Lilly with grants paid to the Karolinska Institutet. Antti Tanskanen reported serving as a member of advisory board for Janssen-Cilag. Erik Jedenius, Dana Enkusson, Amy Leval, and Jan Sermon are employed by Janssen Cilag Pharmaceuticals. Ellenor Mittendorfer-Rutz reports no conflict of interest.

UNIVERSITY OF EASTERN FINLAND

Karolinska Institutet

Stockholms läns landsting

jari.tiihonen@.ki.se