ORIGINAL ARTICLE

# Polypharmacy With Antipsychotics, Antidepressants, or Benzodiazepines and Mortality in Schizophrenia

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**Context:** Polypharmacy is widely used in the treatment of schizophrenia, although it is believed to have major adverse effects on the well-being of patients.

**Objective:** To investigate if the use of benzodiazepines, antidepressants, or multiple concomitant antipsychotics is associated with increased mortality among patients with schizophrenia.

**Design:** Registry-based case linkage study.

**Setting:** Academic research.

**Patients:** We linked national databases of mortality and medication prescriptions among a complete nationwide cohort of 2588 patients hospitalized in Finland for the first time with a diagnosis of schizophrenia between January 1, 2000, and December 31, 2007.

**Main Outcome Measures:** Hazard ratios (HRs) were computed for all-cause mortality during the use of antipsychotics, antidepressants, or benzodiazepines in outpatient care, adjusting for the effects of sociodemographic and clinical variables, geographic location, and current and past pharmacological treatments.

**Results:** Compared with antipsychotic monotherapy, concomitant use of 2 or more antipsychotics was not associated with increased mortality (HR, 0.86; 95% CI, 0.51-1.44). Similarly, antidepressant use was not associated with a higher risk for mortality (HR, 0.57; 95% CI, 0.28-1.16) and was associated with markedly decreased suicide deaths (HR, 0.15; 95% CI, 0.03-0.77). However, benzodiazepine use was associated with a substantial increase in mortality (HR, 1.91; 95% CI, 1.13-3.22), and this was attributable to suicidal deaths (HR, 3.83; 95% CI, 1.45-10.12) and to nonsuicidal deaths (HR, 1.60; 95% CI, 0.86-2.97). In total, 826 of 904 patients (91.4%) who used benzodiazepines had purchased prescriptions that contained more than 28 defined daily doses, violating treatment guidelines.

**Conclusions:** Benzodiazepine use was associated with a marked increase in mortality among patients with schizophrenia, whereas the use of an antidepressant or several concomitant antipsychotics was not. Antidepressant use was associated with decreased suicide deaths. The literature indicates that long-term use of benzodiazepines among patients with schizophrenia is more prevalent in other countries (eg, the United States) compared with Finland, which suggests that benzodiazepine use may contribute to mortality among this patient population worldwide.

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Current guidelines for the pharmacological treatment of schizophrenia recommend antipsychotic monotherapy; concomitant use of more than 1 antipsychotic should be avoided in general practice because of a lack of evidence of increased efficacy and a higher risk for adverse effects.[1] It is unknown if the use of antidepressants or benzodiazepines has beneficial net effects in the treatment of schizophrenia; therefore, no conclusions on their use exist in treatment guidelines.[2-4]

The overall effectiveness of such treatments can be studied by analyzing all-cause mortality because efficacy (as life-years gained) and tolerability (as life-years lost) contribute to the total mortality among patients. This issue has been reported in 2 publications that link nationwide databases of hospital treatment, medication prescriptions, and mortality registers.[5,6] In the Finnish study,[5] the use of any antipsychotic was associated with lower mortality compared with no antipsychotic use, but the effect of concomitant use of several antipsychotics, antidepressants, or benzodiazepines was not studied in detail. In the Danish study,[6] the effect of antidepressant use was not studied, but it was observed that antipsychotic polypharmacy did not contribute to excess mortality from natural causes, while benzodiazepine use was associated with increased risk for mortality. Although these 2 pharmacoepidemiological studies[5,6] adjusted for confounding fac-

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tors to minimize the effects of selection bias, they had some important weaknesses. Both studies included all patients, regardless of whether they were long-term or recently diagnosed cases, which leads to survival bias (ie, only those patients who tolerated the specific treatments and were are alive at the beginning of the follow-up period were included). In the Danish study,[6] the definition of medication exposure was at least 1 prescription filled within 90 days before the date of death or the index date. For example, it was unknown if a patient was currently using a benzodiazepine at the time of death or if the use had been stopped a few days or a few months earlier. Therefore, increased mortality could be explained by the use or lack of use of benzodiazepines.

Consequently, it is unknown if the use of benzodiazepines, antidepressants, or multiple concomitant antipsychotics is associated with increased all-cause mortality among patients with schizophrenia. We studied this issue by linking national databases of mortality and medication prescriptions among a nationwide cohort of 2588 patients who were hospitalized in Finland for the first time with a diagnosis of schizophrenia between January 1, 2000, and December 31, 2007 (mean follow-up period, 4.2 years). Hazard ratios (HRs) were computed for all-cause mortality during the use of antipsychotics, antidepressants, or benzodiazepines in outpatient care, while adjusting for the effects of sociodemographic and clinical variables, geographic location, and current and past somatic and psychotropic pharmacological treatments.

## METHODS

### STUDY DESIGN

The study population has been previously described.[7] In brief, this was a register-based case linkage study among all residents of Finland aged 16 to 65 years who had an initial hospitalization with a diagnosis of schizophrenia (*International Statistical Classification of Diseases, 10th Revision* [*ICD-10*] code F20) between January 1, 2000, and December 31, 2007, and who had not obtained (ie, purchased) any antipsychotic prescription (Anatomic Therapeutic Chemical code N05A) within 6 months before admission. The study cohort was identified from the Finnish National Hospital Discharge Register, which is administered by the National Institute for Health and Welfare (research permission DNRO 206/5.05.00/2009). The basic method of collecting data was similar to that in previous studies.[5,7-9] A total of 33 318 patients had at least 1 hospitalization for a schizophrenia-related illness (*ICD-10* codes F20-F25) during the study period. Of these, 7434 had their initial hospitalization during that period, and 2588 had a strictly defined diagnosis of schizophrenia (*ICD-10* code F20) during their first hospitalization.

The hospitalization data included the start and end dates of hospitalization, the *ICD-10* diagnosis code, and the hospital district in Finland. It has been estimated that more than 90% of patients with schizophrenia are admitted to a hospital at least once in Finland.[10] The validity of schizophrenia diagnoses in the Finnish database has been demonstrated.[10-13] Ethical approval was obtained from all institutions participating in the study and from the Finnish Ministry of Social Affairs and Health.

Information on medication use was obtained from the prescription database of the Social Insurance Institute (research permission KELA 14/522/2009), which covers all residents of Finland. These data contained the date of prescription purchase, the Anatomic Therapeutic Chemical code, and the purchased quantity, stated as the number of defined daily doses (DDDs), which are defined by the World Health Organization.[14]

Discontinuation of medication was defined as the absence of any purchase of a prescription for the same medication within the duration of the previous prescription. The duration of the prescription was calculated by dividing the total amount of medication (in milligrams) of the prescription by the DDD (Anatomic Therapeutic Chemical codes and DDDs for antipsychotics, benzodiazepines, and antidepressants are listed in the eTable [available at: http://www.archgenpsychiatry.com]). For example, if the prescription contained twenty-eight 10-mg tablets of olanzapine, the duration of the prescription would be the total amount ($28 \times 10$ mg = 280 mg) divided by the DDD (10 mg/d), which equals 28 days. To avoid minor deviations from the normal range of consumption (1 DDD/d) being classified as discontinuation (eg, because of slightly lower dosages or short delays in collecting the next prescription), the duration of a treatment period was calculated prospectively by adding 1.15 times the number of the DDD along with an extra 14 days to the date of purchase for each prescription.[15,16] Therefore, if the patient purchased a prescription equal to 14 DDDs on a regular basis, the respective treatment period would be 14 days times 1.15 plus 14 days, which equals 30.1 days, and would not be recorded as discontinuous if the patient collected the next prescription within 30 days. With this procedure, to be classified as adherent to treatment, a patient having a prescription for 30 DDDs must collect the next prescription within 48.5 days ($30 \text{ days} \times 1.15 + 14$ days) after collecting the first prescription, and a patient having a prescription for 60 DDDs must collect the next one within 83 days ($60 \text{ days} \times 1.15 + 14$ days) after the first prescription. These cutoff periods correspond to 46.7% (14 of 30 days), 61.2% (30 of 49 days), and 72.3% (60 of 83 days) use of the DDD. For example, this means that a patient using olanzapine is classified as a continuous user if he or she collects successive prescriptions within 30-day intervals and consumes on average at least 4.7 mg/d of olanzapine ($\geq$6.1 mg/d when collecting prescriptions within 49-day intervals or $\geq$7.2 mg/d when collecting prescriptions within 83-day intervals). The same procedure was used for oral and long-acting injection medications. The proportion of long-acting injection medications was 960 of 6260 person-years (15.3%) of all antipsychotic use during the entire follow-up period. Because no data on pharmacological treatment during hospitalization are documented in the national prescription databases, we calculated the risk for mortality with inclusion and exclusion of hospital deaths and person-years.

In Finland, patients are usually only given a few days' supply (ie, $<$1 week) of an antipsychotic, antidepressant, or benzodiazepine when discharged from the hospital. On leaving the hospital, patients receive a prescription to collect their medication from a pharmacy outside of the hospital. In Finland, legislation does not allow compulsory treatment in outpatient care.

The use of the following drugs was recorded in the study: antipsychotics, antidepressants, benzodiazepines, analgesics, antiparkinsonian drugs, lipid-modifying agents, blood glucose–lowering drugs, and drugs used to treat addictive disorders. Prescription data were obtained from January 1, 2000, to December 31, 2007, and from the 4-year period before the start of the study (January 1, 1996, to December 31, 1999) to account for the number of previous treatments. The mortality data were obtained from Statistics Finland (research permission TK-53-739-09). Data on causes of death were based on *ICD-10* codes that were recorded in death certificates. In accord with Finnish legislation, all deaths that are sudden or suspected to be unnatural are subject to forensic autopsy. Therefore, all diagno-



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**Table 1. Characteristics of 2588 Patients With Schizophrenia in the Cohort**

| Characteristic | No. of Events per Person-years | Crude Mortality Rate (95% CI) per 1000 Person-years[a] |
|---|---|---|
| **Medication Use at the Time of Death** | | |
| Benzodiazepines | | |
| No | 134/9612 | 13.9 (11.7-16.5) |
| Yes | 26/1157 | 22.5 (15.3-33.0) |
| Antipsychotics | | |
| No | 96/4509 | 21.3 (17.4-26.0) |
| Yes | 64/6259 | 10.2 (8.0-13.0) |
| Antidepressants | | |
| No | 146/9063 | 16.1 (13.7-18.9) |
| Yes | 14/1706 | 8.2 (4.9-13.8) |
| Drugs used to treat addictive disorders | | |
| No | 157/10 685 | 14.7 (12.6-17.2) |
| Yes | 3/83 | 36.1 (11.6-111.9) |
| Analgesics | | |
| No | 159/10 742 | 14.8 (12.7-17.3) |
| Yes | 1/26 | 38.5 (5.4-273.3) |
| Antiparkinsonian drugs | | |
| No | 157/10 668 | 14.7 (12.6-17.2) |
| Yes | 3/101 | 29.7 (9.6-92.1) |
| Blood glucose–lowering drugs | | |
| No | 156/10 568 | 14.8 (12.7-17.3) |
| Yes | 4/201 | 19.9 (7.5-53.0) |
| Lipid-modifying agents | | |
| No | 156/10 552 | 14.8 (12.7-17.3) |
| Yes | 4/217 | 18.4 (6.9-49.0) |
| **Background Effects** | | |
| Hospitalization | | |
| No | 144/9872 | 14.6 (12.4-17.2) |
| Yes | 16/897 | 17.8 (10.9-29.1) |
| Sex | | |
| Male | 108/6553 | 16.5 (13.7-19.9) |
| Female | 52/4216 | 12.3 (9.4-16.1) |
| Age category, y | | |
| 16-25 | 24/2775 | 8.6 (5.8-12.8) |
| 26-35 | 24/2559 | 9.4 (6.3-14.0) |
| 36-45 | 19/2001 | 9.5 (6.1-14.9) |
| 46-55 | 46/2217 | 20.7 (15.5-27.6) |
| 56-65 | 47/1217 | 38.6 (29.0-51.4) |
| Hospital district in Finland | | |
| Helsinki | 61/4411 | 13.8 (10.7-17.7) |
| Turku | 19/1196 | 15.9 (10.1-24.9) |
| Tampere | 34/2169 | 15.7 (11.2-22.0) |
| Kuopio | 27/1616 | 16.7 (11.5-24.4) |
| Oulu | 19/1377 | 13.8 (8.8-21.6) |

[a]Mortality rates were 16 deaths per 1153 person-years (13.9; 95% CI, 8.5-22.7 per 1000 person-years) during first-generation antipsychotic use and 54 deaths per 5503 person-years (9.8; 95% CI, 7.5-12.8 per 1000 person-years) during second-generation antipsychotic use (6 deaths during concomitant first-generation antipsychotic and second-generation antipsychotic use).

ses of unnatural deaths (including suicides) are based on forensic autopsy findings. The validation of suicide diagnosis has not been published, but the rate of forensic autopsies in Finland (24.3% of all deaths) is high compared with than in other European countries.[17]

In the mortality analysis for each patient, the follow-up period was prospectively divided into intervals. For each demarcated interval, medication treatments were classified as currently active or not. Because patients may switch their medications, a patient could contribute to several risk sets in the analysis (eg, using 2 antipsychotics, a benzodiazepine, and no antidepressant for the first 5 months; then using a benzodiazepine, no antipsychotic, and no antidepressant for 7 months; and then using an antipsychotic, an antidepressant, and no benzodiazepine for 15 months).

## STATISTICAL ANALYSIS

The primary outcome measures of interest were risk of death (1) during current use of 2 or more antipsychotics vs antipsychotic monotherapy, (2) during current antidepressant use vs no antidepressant use, and (3) during current benzodiazepine use vs no benzodiazepine use. The secondary outcome measures were the corresponding risk for suicide death and the comparison risk for mortality during current use of 2 or more antipsychotics vs no antipsychotic use. In these analyses, current use of a drug represents the person-time during which continuous exposure to a drug occurs. The follow-up period for each patient began at the end of the first hospitalization. The end of the follow-up period for the whole study was December 31, 2007. The follow-up period for each patient ended at the date of death or at the end of the study period. Crude relative risks (95% CIs) were calculated for the various antipsychotic, antidepressant, and benzodiazepine treatment patterns. A stratified Cox proportional hazards model was used to assess the HRs using hospital districts in Finland as the strata. The following baseline variables were included in the Cox proportional hazards model for all outcomes studied: sex, age at diagnosis, and the duration of the first hospitalization. Similarly, the following time-dependent variables were included for all outcomes: current and past use of antipsychotics, antidepressants, benzodiazepines, analgesics, antiparkinsonian drugs, lipid-modifying agents, blood glucose–lowering drugs, and drugs used to treat addictive disorders. The resulting HRs (95% CIs) were reported. Because this was an observational study (including all new patients with schizophrenia in Finland) and because the number of events was not known beforehand, no a priori power analysis was conducted. Using the marginal structural modeling approach,[18] we assessed the robustness of the conventional Cox proportional hazards model toward possible time-dependent confounding bias due to previous treatments affecting both the subsequent treatment and outcome.

## RESULTS

The mean (SD) age of the study population was 37.8 (13.7) years, and 1604 of 2588 patients (62.0%) were male. The mean (SD) follow-up period was 4.2 (2.2) years. The person-years, number of events, and crude rates for the cohort are summarized in **Table 1**. Among 160 deaths, 16 occurred during hospital treatment (median duration of hospitalization at the time of death, 30.5 days). The total duration of hospitalization was 897 person-years (8.3%).

The results for all-cause mortality are given in **Table 2**. Current use of 2 or more antipsychotics (vs antipsychotic monotherapy) was not associated with increased risk for mortality, while no antipsychotic use was associated with significantly higher mortality (HR, 2.09; 95% CI, 1.34-3.26). The HR for current use of 2 or more antipsychotics (vs no antipsychotic use) was 0.41 (95% CI, 0.25-0.68). Although the risk for mortality was 43% lower (HR, 0.57; 95% CI, 0.28-1.16) during antidepressant use (vs no antidepressant use), it was 91% higher (HR, 1.91;



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**Table 2. All-Cause Mortality[a]**

| Variable | Hazard Ratio (95% CI) | *P* Value |
|---|---|---|
| **Background Effects** | | |
| Sex, male vs female | 1.70 (1.19-2.44) | .004 |
| Age at diagnosis | 1.04 (1.03-1.06) | <.001 |
| Duration of first hospitalization | 1.00 (1.00-1.00) | .23 |
| Current use | | |
| Drugs used to treat addictive disorders | 4.44 (0.92-21.50) | .06 |
| Analgesics | 1.56 (0.20-12.44) | .68 |
| Antiparkinsonian drugs | 1.51 (0.44-5.17) | .51 |
| Blood glucose–lowering drugs | 1.75 (0.40-7.69) | .46 |
| Lipid-modifying agents | 0.38 (0.10-1.44) | .15 |
| Past use | | |
| Antipsychotics | 1.00 (0.99-1.01) | .65 |
| Benzodiazepines | 0.99 (0.97-1.01) | .41 |
| Antidepressants | 1.00 (0.97-1.04) | .93 |
| Drugs used to treat addictive disorders | 1.00 (0.77-1.30) | .99 |
| Analgesics | 1.01 (0.92-1.10) | .84 |
| Antiparkinsonian drugs | 1.01 (0.97-1.05) | .76 |
| Blood glucose–lowering drugs | 0.95 (0.85-1.05) | .31 |
| Lipid-modifying agents | 1.11 (1.05-1.18) | <.001 |
| No. of hospitalizations after January 1, 2000 | 1.02 (0.98-1.06) | .38 |
| **Primary Outcome Measures of Interest** | | |
| Current use of ≥2 antipsychotics, vs antipsychotic monotherapy | 0.86 (0.51-1.44) | .56 |
| Current benzodiazepine use, vs no benzodiazepine use | 1.91 (1.13-3.22) | .02 |
| Current antidepressant use, vs no antidepressant use | 0.57 (0.28-1.16) | .12 |

[a]All variables were included in the model simultaneously. In a secondary analysis, current antidepressant use was associated with significantly lower all-cause mortality compared with current benzodiazepine use (*P* = .009).

**Table 3. Polypharmacy Treatment Patterns and Total Mortality Rates**

| Polypharmacy Combination Pair[a] | No. of Events per Person-years | Total Mortality Rate (95% CI) per 1000 Person-years |
|---|---|---|
| No antipsychotic use and no antidepressant use | | |
| With no benzodiazepine use | 82/4049 | 20.3 (16.3-25.2) |
| With current benzodiazepine use | 9/169 | 53.3 (27.7-102.4) |
| No antipsychotic use and current antidepressant use | | |
| With no benzodiazepine use | 4/241 | 16.6 (6.2-44.2) |
| With current benzodiazepine use | 1/50 | 20.0 (2.8-142.0) |
| Current use of 1 antipsychotic and no antidepressant use | | |
| With no benzodiazepine use | 21/2127 | 9.9 (6.5-15.2) |
| With current benzodiazepine use | 7/248 | 28.2 (13.4-59.2) |
| Current use of 1 antipsychotic and current antidepressant use | | |
| With no benzodiazepine use | 2/515 | 3.9 (1.0-15.6) |
| With current benzodiazepine use | 1/99 | 10.1 (1.4-71.7) |
| Current use of ≥2 antipsychotics and no antidepressant use | | |
| With no benzodiazepine use | 21/2050 | 10.2 (6.7-15.6) |
| With current benzodiazepine use | 6/420 | 14.3 (6.4-31.8) |
| Current use of ≥2 antipsychotics and current antidepressant use | | |
| With no benzodiazepine use | 4/631 | 6.3 (2.4-16.8) |
| With current benzodiazepine use | 2/171 | 11.7 (2.9-46.8) |

[a]In all polypharmacy combination-pairs, current benzodiazepine use was associated with higher mortality rates.

95% CI, 1.13-3.22) during benzodiazepine use (vs no benzodiazepine use) (*P* = .009 for the difference in HRs for antidepressant vs benzodiazepine use). When the marginal structural model was applied, the HRs were 1.80 (95% CI, 1.02-3.20) for benzodiazepine use (vs no benzodiazepine use) and 0.63 (95% CI, 0.24-1.65) for antidepressant use (vs no antidepressant use).

The HRs for suicide were 0.87 (95% CI, 0.32-2.34) for current use of 2 or more antipsychotics, 0.15 (95% CI, 0.03-0.77) for current antidepressant use, and 3.83 (95% CI, 1.45-10.12) for current benzodiazepine use. For all other (nonsuicidal) deaths, the HRs were 0.88 (95% CI, 0.48-1.63) for current use of 2 or more antipsychotics, 0.87 (95% CI, 0.39-1.92) for current antidepressant use, and 1.60 (95% CI, 0.86-2.97) for current benzodiazepine use.

When durations of hospitalization were not censored (ie, all deaths were included in the analysis), the following HRs for all-cause mortality were obtained: 1.00 (95% CI, 0.60-1.66) for current use of 2 or more antipsychotics, 2.04 (95% CI, 1.32-3.14) for no antipsychotic use, 0.57 (95% CI, 0.30-1.08) for current antidepressant use, and 1.80 (95% CI, 1.10-2.95) for current benzodiazepine use.

Polypharmacy treatment patterns and total mortality rates are given in **Table 3**. In all combinations, current benzodiazepine use was associated with higher mortality compared with no benzodiazepine use, regardless of concomitant use or nonuse of antipsychotics or antidepressants. Conversely, in all pairwise comparisons, current antidepressant use (vs no antidepressant use) and antipsychotic use (vs no antipsychotic use) were associated with lower mortality (ie, the effect of psychotropic drugs was similar in all combinations, and no substantial interactions were observed). The highest mortality rate was seen for the combination of no antipsychotic use, no antidepressant use, and current benzodiazepine use, which was in line with the observations of a good outcome associated with antidepressant use and antipsychotic use and a poor outcome associated with benzodiazepine use among this patient population.

Causes of death during benzodiazepine use vs no benzodiazepine use are given in **Table 4**. No statistically significant differences were observed in the proportions of causes of deaths between deaths during benzodiazepine use vs deaths during no nonbenzodiazepine use. The mean (SD) ages at the start of the follow-up period were 43.2 (15.2) years among patients with deaths during benzodiazepine use and 45.9 (14.0) years among patients with deaths during no benzodiazepine use (*P* = .48, Wilcoxon 2-sample test); among suicidal deaths, the mean (SD) ages were 29.6 (9.3) and 31.6 (11.3) years, respectively (*P* = .92, Wilcoxon 2-sample test). Twenty-one of 26 deaths (80.8%) during benzodiazepine use (5 of 7 sui-



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**Table 4. Causes of Death During Benzodiazepine Use vs No Benzodiazepine Use**

| Cause of Death[a] | Deaths, No. (%) Total (n = 160) | During No Benzodiazepine Use (n = 134) | During Current Benzodiazepine Use (n = 26) |
|---|---|---|---|
| Infectious and parasitic diseases | **2** (1.3) | 1 (0.7) | 1 (3.8) |
| Neoplasms | **30** (18.8) | 25 (18.7) | 5 (19.2) |
| Endocrine, nutrition, and metabolic diseases | **4** (2.5) | 4 (3.0) | 0 |
| Mental and behavioral disorders | **4** (2.5) | 4 (3.0) | 0 |
| Diseases of the nervous system | **3** (1.9) | 2 (1.5) | 1 (3.8) |
| Diseases of the circulatory system | **35** (21.9) | 33 (24.6) | 2 (7.7) |
| Diseases of the respiratory system | **7** (4.4) | 5 (3.7) | 2 (7.7) |
| Diseases of the digestive system | **9** (5.6) | 6 (4.5) | 3 (11.5) |
| Diseases of the musculoskeletal system and connective tissue | **1** (0.6) | 1 (0.7) | 0 |
| Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified | **7** (4.4) | 7 (5.2) | 0 |
| External causes of morbidity and mortality | **57** (35.6) | 45 (33.6) | 12 (46.2) |
| Suicidal deaths | **35** (21.9) | 28 (20.9) | 7 (26.9) |
| Accidental and violent deaths, including accident, drowning, poisoning, and homicide | **22** (13.8) | 17 (12.7) | 5 (19.2) |
| Unknown | **1** (0.6) | 1 (0.7) | 0 |

[a]Causes of death are *International Statistical Classification of Diseases, 10th Revision* classifications.

cidal deaths) occurred during treatment periods in which the prescriptions contained more than 28 DDDs. Overall, 904 of 2588 patients (34.9%) had used benzodiazepines, and 826 of them (91.4%) had purchased prescriptions that contained more than 28 DDDs, which violates current treatment guidelines. The median duration of benzodiazepine use was 58 days (interquartile range, 35-116 days). Mortality rates (in descending order per 1000 person-years) for specific benzodiazepine derivates were as follows: 9 deaths per 291 person-years (30.9; 95% CI, 16.1-59.4) for temazepam, 5 deaths per 165 person-years (30.3; 95% CI, 12.6-72.8) for diazepam, 4 deaths per 137 person-years (29.2; 95% CI, 11.0-77.8) for oxazepam, 1 death per 41 person-years (24.4; 95% CI, 3.4-173.2) for zolpidem tartrate, 5 deaths per 234 person-years (21.4; 95% CI, 8.9-51.4) for zopiclone, 3 deaths per 250 person-years (12.0; 95% CI, 3.9-37.2) for lorazepam, 0 deaths per 43 person-years for alprazolam, 0 deaths per 19 person-years for nitrazepam, and 0 deaths per 9 person-years for chlordiazepoxide. The use of other benzodiazepine agents indicated for anxiety or sleeping problems (triazolam, midazolam maleate, and zaleplon) was negligible. Clonazepam (Anatomic Therapeutic Chemical code N03AE01) is only indicated for epilepsy in Finland, and the total use of clonazepam in Finland is less than 2% of all benzodiazepine use. One death occurred during concomitant use of oxazepam and temazepam.

## COMMENT

To our knowledge, this is the first study to examine antipsychotic, antidepressant, and benzodiazepine polypharmacy and all-cause mortality among patients with schizophrenia using information on current medication use and adjusting for the effects of sociodemographic and clinical variables and current and past pharmacological treatments. These results reveal that benzodiazepine use is associated with substantially increased risk for mortality among this population, while antidepressant use or concomitant use of several antipsychotics was not associated with increased mortality.

One other study[6] to date has investigated polypharmacy and mortality in schizophrenia using nationwide databases. Our results resemble those reported by Baandrup et al,[6] who observed that the use of several antipsychotics was associated with about the same mortality as the use of one antipsychotic and with markedly lower mortality than no antipsychotic use. This Danish study also observed substantially increased risk for mortality among patients who were treated with benzodiazepines, as we did, although there were methodological differences between the 2 studies. While we calculated the status of current medication use at each time point (date) and used previous (discontinued) use as a covariate in the analysis, Baandrup et al defined current medication use as at least 1 prescription filled within 90 days before the date of death or the index date. This may have caused some mislabeling, especially with benzodiazepine use, because current guidelines recommend that the maximum duration of use should be 3 to 4 weeks. Another crucial methodological issue is that the Danish study included all registered patients with schizophrenia aged 18 to 53 years in Denmark, while we studied only those new patients in Finland who were diagnosed as having schizophrenia between January 1, 2000, and December 31, 2007. The reason for excluding more long-term patients in our study was to avoid survival bias. However, when considering these methodological differences, the mortality results during antipsychotic and benzodiazepine treatments obtained in Finland and Denmark were almost identical in the 2 studies.

Patients may use higher doses of benzodiazepines than 1 DDD, and if they do not obtain a new prescription when the medication has run out sooner than expected, they



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are classified as using the drug, although they have exhausted their medication supply. In such cases, it is probable that patients experience severe withdrawal symptoms, and the putative increased risk for mortality would still be attributable to the preceding high-dose benzodiazepine use. Discontinuation of long-term benzodiazepine use typically results in increased anxiety, which may contribute to suicidal behavior. However, our study was not designed to investigate this issue, and evaluation of causality and mechanisms of benzodiazepine-related mortality requires more comprehensive clinical data.

Mood stabilizers, such as valproic acid, carbamazepine, lithium carbonate, lamotrigine, and topiramate, are also used among patients with schizophrenia. The primary indication for most of these compounds is epilepsy, and this group of drugs is heterogeneous in clinical effects and in pharmacological mechanisms of action. Because lumping these compounds together would not have been useful and because studying each compound separately would have been complicated, they were not included in the analysis, which is a limitation of our study. Also, for practical reasons it was not possible to include antihypertensive use, epilepsy, or diet-controlled type 2 diabetes mellitus as covariates in the study.

We observed no increased mortality during concomitant use of several antipsychotics compared with antipsychotic monotherapy, which was the same result reported by Baandrup et al.[6] Although it is widely believed that antipsychotic polypharmacy increases mortality, there are no methodologically sound studies available to date that are based on data from filled prescriptions to support this assumption. Only 2 studies have reported a positive correlation with mortality: one study[19] investigated the maximum number of concomitant antipsychotics used during a 10-year follow-up period, and the other study[20] evaluated the number of antipsychotics used at baseline in a 17-year follow-up period. Because these studies were based on case records, their results may reveal associations between mortality and the number of antipsychotic prescriptions obtained several years before the death, rather than actual current or past antipsychotic use.

In the present study, 10% of deaths occurred during hospitalization, and 5% occurred more than 30 days after start of hospitalization. Because no data on pharmacological treatment during hospitalization are documented in the national prescription databases, we calculated the risk for mortality with inclusion and exclusion of hospital deaths and person-years. The HRs were almost the same for both methods. The mean age of patients in the present study was 37.8 years. This older age is probably due to delays in settling on a strictly defined diagnosis of schizophrenia, and this issue has been discussed in detail in previous study.[7] Although we excluded patients who had received any antipsychotic treatment during the 6 months preceding the onset of the follow-up period (ie, their first hospitalization with a diagnosis of schizophrenia), many patients had probably been previously treated in outpatient care and had used psychotropic medication periodically. Therefore, we were unable to fully exclude survival bias. However, if it would have been possible to eliminate survival bias totally, the excess mortality risk would have obviously been even higher among those patients who were using benzodiazepines.

There is a good correlation between the treatment effects of randomized and nonrandomized studies.[21] However, selection bias is a major issue in observational studies, regardless of how refined the statistical methods and adjustment of the confounding factors are. In our study population, it is obvious that patients receiving additional medications, such as a second or third antipsychotic, an antidepressant, or benzodiazepines, are more severely ill than patients receiving only antipsychotic monotherapy. Although particular characteristics of the patients' treatments were taken into account by adjusting the effects of clinical and sociodemographic variables, geographic location, and current and past use of somatic and psychotropic medications, data on many potentially important confounding variables, such as smoking, substance abuse, and body mass index, were unavailable. While this adjustment may not have fully eliminated the effect of selection bias, it is remarkable to see that even the crude rates for mortality showed that the use of antipsychotics and antidepressants was associated with decreased mortality, while the use of benzodiazepines demonstrated marked increase in mortality for all combinations of these drug categories. When the robustness of the conventional Cox proportional hazards model toward possible time-dependent confounding bias due to previous treatments affecting both the subsequent treatment and outcome was assessed using marginal structural modeling,[18] the HR for benzodiazepine use did not change significantly.

In a secondary analysis, current antidepressant use was associated with significantly lower all-cause mortality compared with current benzodiazepine use. Current antidepressant use was also associated with substantially decreased suicide deaths, whereas current benzodiazepine use was associated with marked increased risk for suicide. Because depressed, suicidal, and anxious patients are more likely than other patients to receive both antidepressants and benzodiazepines, the observed effect from these 2 classes of drugs may differ considerably in that antidepressant use may be beneficial and benzodiazepine use may be harmful in the treatment of patients with schizophrenia after their first hospitalization (but not necessarily among stabilized long-term patients[22]). Moreover, catatonia and sleeping problems are 2 symptoms that might be more common among patients who receive benzodiazepines than among patients who receive antidepressants. While only 2% of suicide patients with schizophrenia were diagnosed as having a *DSM-III-R* catatonic subtype condition in a nationwide Finnish psychological autopsy study,[23] catatonic symptoms probably occur more often. Sleeping problems are treated with short-acting anxiolytics, such as zopiclone and zolpidem tartrate. Our results demonstrate that these medications were not associated with a higher mortality rate than long-acting diazepam, which indicates that patients' sleeping problem characteristics do not explain the results. However, it should be noted that all polypharmacy increases the risk for drug-drug interactions and the adverse effect burden, which could not be assessed in this study. Our findings are in line with the re-



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sults of other studies[24-27] that suggest antidepressants may enhance the therapeutic effects of antipsychotics, which may be relevant to reduce mortality risk. To avoid a more complicated analysis and numerous comparisons, we did not study specific antidepressant agents. Previous results revealed no marked differences in the beneficial effects of antidepressants on total mortality among suicidal patients with schizophrenia.[28]

During benzodiazepine treatment, mortality was increased because of suicidal deaths (283% increase) and nonsuicidal deaths (60% increase). More than 80% of all deaths occurred during treatment periods with prescriptions that included more than 28 DDDs of benzodiazepines, and more than 90% of patients used benzodiazepines on a long-term basis. Such long-term use results in tolerance, dose escalation, and eventual withdrawal symptoms when the treatment medication is stopped abruptly, typically when the medication has run out before the next prescription is scheduled. It was not possible to adjust for the effect of substance abuse, other than including data on drugs used to treat addictive disorders, because secondary diagnoses, such as substance abuse, are typically underdiagnosed in the Finnish National Hospital Discharge Register for patients with schizophrenia. Although substance abuse and dependence are considered contraindications for prescribing benzodiazepines, it probably happens frequently, and concomitant use of benzodiazepines, alcohol, and illicit drugs may explain some deaths from accidents and poisonings. Benzodiazepine use induces impulsive and aggressive behaviors among patients with borderline personality disorder,[29] predisposing such patients to violent and accidental deaths. This may be an explanation underlying the high mortality seen with benzodiazepine use among patients with schizophrenia. In addition, benzodiazepine use may contribute to accidents at work and in traffic. Sleeping problems, such as sleep apnea, might also contribute to daytime sedation, but our database did not include this diagnostic category. Recent investigations and a systematic review found that, in general, regular benzodiazepine use is associated with increased mortality risk.[30-32]

Although long-term benzodiazepine use (in violation of treatment guidelines) was common in our study population, the literature indicates that it is probably more common among patients with schizophrenia in other developed countries, such as the United States.[33,34] This suggests that benzodiazepine use may contribute to mortality, especially violent and accidental deaths, among this patient population worldwide.

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