Antipsychotic Polypharmacy and Risk of Death From Natural Causes in Patients With Schizophrenia: A Population-Based Nested Case-Control Study

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Objective: Concomitant prescription of more than 1 antipsychotic agent (antipsychotic polypharmacy) in the treatment of schizophrenia is prevalent, although monotherapy is generally recommended. Mortality from natural causes is markedly increased in schizophrenia, and the role of polypharmacy remains controversial. The objective was to investigate if antipsychotic polypharmacy is associated with the excess mortality from natural causes among patients with schizophrenia.

Method: A population-based nested case-control study was conducted using patient data from January 1, 1996, to December 31, 2005, obtained from central Danish registers. From the study population of 27,633 patients with *ICD-8*– and *ICD-10*–diagnosed schizophrenia or other mainly nonaffective psychoses, aged 18–53 years, we identified 193 cases who died of natural causes within a 2-year period and 1,937 age- and sex-matched controls. Current drug use was defined as at least 1 prescription filled within 90 days before the date of death or the index date. The data were analyzed by conditional logistic regression.

Results: Risk of natural death did not increase with the number of concurrently used antipsychotic agents compared with antipsychotic monotherapy (no antipsychotics: adjusted odds ratio [OR] = 1.48 [95% CI, 0.89–2.46]; 2 antipsychotics: OR = 0.91 [95% CI, 0.61–1.36]; 3 or more antipsychotics: OR = 1.16 [95% CI, 0.68–2.00]). Current use of benzodiazepine derivatives with long elimination half-lives (more than 24 hours) was associated with increased risk of natural death in patients with schizophrenia treated with antipsychotics (OR = 1.78 [95% CI, 1.25–2.52]).

Conclusions: Antipsychotic polypharmacy did not contribute to the excess mortality from natural causes in middle-aged patients with schizophrenia. The detected increased risk of death associated with benzodiazepines with long elimination half-lives calls for further clarification.

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Several surveys[1–3] addressing the psychopharmacologic treatment of patients with schizophrenia have highlighted an expanding discrepancy between prescription patterns in clinical practice and recommendations in various prescribing guidelines. There is broad agreement that antipsychotic polypharmacy (concomitant prescription of more than 1 antipsychotic agent) should generally be avoided because of lack of evidence of superior efficacy, increased occurrence of adverse effects, increased costs, and scarce knowledge of safety.[4,5] Antipsychotic polypharmacy may be an option, but only for patients who do not respond to monotherapy with clozapine, and the effect and tolerability should be meticulously monitored.[5,6]

Schizophrenia is associated with mortality rates 2 to 3 times as high as those encountered in the general population.[7] This number is, in part, attributable to an increased suicide rate, but in recent years it has been recognized that the risk of death from natural causes also is increased, accounting for approximately two-thirds of the excess mortality.[7,8] The origin of this excess mortality is not fully understood, but concern has been raised over the impact of unhealthy lifestyle (smoking, physical inactivity, poor diet), substance abuse, undiagnosed medical comorbidities, and antipsychotic medication, especially polypharmacy.[7,9,10]

The objective of this study was to investigate the possible association between antipsychotic polypharmacy and mortality from natural causes among patients with schizophrenia.

METHOD

Data Source

This population-based nested case-control study was conducted using Danish central registers encompassing the

whole population of Denmark. These Danish registers draw on a civil registration number that is uniquely assigned to every Danish citizen at birth or immigration, coding his or her date of birth and sex. The civil registration number can, therefore, be used for electronic record linkage among multiple registers. For this study, we used data from the Danish National Patient Register, the Danish Civil Registration System, and the Danish Register of Medicinal Product Statistics between 1996 and 2005.

The Danish National Patient Register records data on all patients admitted to Danish somatic and psychiatric hospitals, emergency rooms, and outpatient clinics. All admissions to hospitals have been registered since 1977. Contacts to emergency units and outpatient clinics have been registered since 1995. Variables include, among others, administrative data, civil registration number, date of admission and discharge, data on hospital and department, and clinical data such as diagnosis codes and operations. All diagnoses were coded according to the World Health Organization *International Classification of Diseases, Eighth Revision (ICD-8)* until December 31, 1993, and have been coded according to the *Tenth Revision (ICD-10)* since this date.[11] The Danish Civil Registration System contains post-1968 information on vital status (dead, alive), date of death, and residence for the entire Danish population.[12]

The Danish Register of Medicinal Product Statistics was initiated in January 1994, is complete from 1995 onward, and it contains individual-based data on prescription drugs obtained from community pharmacies. The data include, among others, information on the dispensed drug (Anatomic Therapeutic Chemical classification code, name, package size, formulation, quantity) and the date of transaction.

Study Population

From the Danish National Patient Register, we identified all patients aged 18–53 years as of January 1, 2004 with a registered diagnosis of schizophrenia or other mainly nonaffective psychotic disorders (*ICD-10*: F20-29) between January 1, 1996, and December 31, 2005. Both main and auxiliary diagnoses were used. Patients most recently registered with a diagnosis of mania (*ICD-10*: F30) or bipolar affective disorder (*ICD-10*: F31) were not included.

Selection of Cases and Controls

We identified all patients from the study population who died between January 1, 2004, and December 31, 2005, using the Danish Civil Registration System. The manner of death was identified from the death certificates and cases were defined as patients who died of natural causes. Patients who died of suicide, homicide, or an accident or patients for whom the manner of death was unknown were excluded.

We aimed to select 15 age- and sex-matched controls per case from the study population. Controls had to be alive at the date of death of the respective cases and were assigned this date as the index date. Cases and controls were only included if they had filled at least 1 prescription for an antipsychotic and had been hospitalized for less than 240 days during the year prior to the date of death or the index date. Furthermore, cases and controls had to have had their first entry in the Danish National Patient Register at least 365 days prior to the date of death or the index date.

Exposure Definition

From the Danish Register of Medicinal Product Statistics, we defined current drug use as at least 1 prescription filled within 90 days before the date of death or the index date.

Antipsychotics were categorized into first- and second-generation agents, and first-generation antipsychotics further subdivided into high-, medium-, and low-potency agents. Antipsychotic monotherapy was defined as filling of at least 1 prescription for a single antipsychotic within 90 days prior to the date of death or the index date. Antipsychotic polypharmacy was defined as filling of at least 1 prescription for 2 or more different antipsychotics during the 90 days prior to the date of death or the index date and was categorized into polypharmacy with 2 and 3 or more different antipsychotics concurrently.

Comedication

We further assessed psychotropic comedication during the 90 days prior to death or the index date: current use of lithium, antidepressants, benzodiazepine derivatives and related drugs, and antiepileptics. Benzodiazepines were categorized according to their elimination half-lives ($T_{½}$) as follows: long $T_{½}$ (more than 24 hours), intermediate $T_{½}$ (6–24 hours) and short $T_{½}$ (less than 6 hours).

We also determined the number of different drug compounds used for the treatment of somatic disease for which prescriptions were filled during the 90 days prior to death or the index date as a proxy for somatic comorbidity. The number of different somatic comedications was categorized into concomitant use of 0, 1, 2–4, 5–9, and 10 or more different drugs.

Covariates

Substance abuse is associated with both schizophrenia[13] and increased mortality[10] and was, therefore, included as a potential confounder. Patients were defined as substance abusers if they had a drug- (*ICD-10*: F11.0–F16.9; F18.0–F19.9) or alcohol- (*ICD-10*: F10.0–F10.9; K70.0–K70.9; I85.0–I85.9) related diagnosis of abuse recorded in the Danish National Patient Register and/or any prescriptions for the treatment of drug or alcohol abuse recorded in the Danish Register of Medicinal Product Statistics. Substance abuse based on such prescriptions (methadone or drugs used in alcohol dependence) required more than 1 prescription for these drugs between 2003 and 2005 and did not include patients using methadone as an analgesic.

A diagnosis of epilepsy (*ICD-10*: G40–41) was identified from the Danish National Patient Register because it is an

independent risk factor for premature death.[10] Epilepsy is also associated with increased risk of psychosis[14] and it was, therefore, adjusted for in the analyses.

Psychiatric morbidity, living circumstances, and other social environment factors are known to vary between urban and rural areas.[15] Moreover, treatment patterns for schizophrenia may differ between regions and we, therefore, included place of residence (capital region vs the rest of Denmark) as a potential confounder.

Statistical Methods

We performed conditional logistic regression analyses to calculate crude and adjusted odds ratios (ORs) and 95% CIs of the association between antipsychotic polypharmacy and natural death compared with antipsychotic monotherapy. Antipsychotic monotherapy was chosen as the reference group since it represents the recommended therapy regimen. We performed a backward stepwise variable selection strategy, starting with the full model including all potential confounders or independent risk factors: current use of lithium, antidepressants, benzodiazepine derivatives and related drugs, antiepileptics, somatic comedication, substance abuse, epilepsy, and place of residence. The *P* value for excluding a variable from the model was fixed at a significance level of $P > .05$. The final model was achieved by entering the variables remaining in the backward selection model (benzodiazepine derivatives and epilepsy), supplementing all antipsychotic and somatic comedication categories. To investigate effect-measure modification, we stratified our analyses by sex and age.

All analyses were performed using Stata/SE 9.0 for Windows (Statacorp LP, College Station, Texas).

RESULTS

We identified 27,633 patients, aged 18–53 years, diagnosed with schizophrenia or other mainly nonaffective psychotic disorders between January 1, 1996, and December 31, 2005. Among those, we identified 193 cases who died between January 1, 2004, and December 31, 2005. We also identified 1,937 matched controls (5–15 per case) fulfilling the inclusion criteria. The patient characteristics are presented in Table 1. Two-thirds of cases and controls were male, and more than 80% were between 40 and 53 years old. Antipsychotic polypharmacy was more frequent among cases than among controls (41% vs 34%). Moreover, more cases than controls used 5 or more different somatic comedications, used benzodiazepine derivatives, and had epilepsy. The higher use of somatic comedications among cases than among controls was most pronounced for cardiovascular drugs (37% vs 16%), antidiabetic drugs (12% vs 6%), opioid analgesics (23% vs 5%), other analgesics and antipyretics (26% vs 8%), anti-inflammatory and antirheumatic products (18% vs 9%), and drugs for obstructive airway diseases (20% vs 6%).

Table 1. Demographic and Clinical Characteristics of Cases and Controls

Characteristic	Cases (N = 193), n (%)	Controls (N = 1,937), n (%)
Sex		
Male	127 (65.8)	1,300 (67.1)
Female	66 (34.2)	637 (32.9)
Age, y		
18–29	5 (2.6)	54 (2.8)
30–39	27 (14.0)	269 (13.9)
40–49	99 (51.3)	1,017 (52.5)
50–53	62 (32.1)	597 (30.8)
Number of concomitant antipsychotic drugs		
0	25 (13.0)	249 (12.9)
1	89 (46.1)	1,026 (53.0)
2	53 (27.5)	501 (25.9)
≥3	26 (13.5)	161 (8.3)
Current use of benzodiazepine derivatives and related drugs	131 (67.9)	932 (48.1)
Long $T_{½}$ (>24 h)[a]	91 (47.2)	479 (24.7)
Intermediate $T_{½}$ (6–24 h)[b]	37 (19.2)	377 (19.5)
Short $T_{½}$ (<6 h)[c]	41 (21.2)	311 (16.1)
Number of somatic comedications		
0	30 (15.5)	673 (34.7)
1	28 (14.5)	495 (25.6)
2–4	46 (23.8)	553 (28.6)
5–9	65 (33.7)	195 (10.1)
≥10	24 (12.4)	21 (1.1)
Substance abuse	89 (46.1)	617 (31.9)
Epilepsy	26 (13.5)	90 (4.7)
Place of residence[d]	80 (41.5)	758 (39.1)

[a]Diazepam, chlordiazepoxide, clobazam, nitrazepam, flunitrazepam, and clonazepam.
[b]Oxazepam, lorazepam, bromazepam, alprazolam, and lormetazepam.
[c]Triazolam, brotizolam, zopiclone, and zolpidem.
[d]Capital region versus rest of Denmark.
Abbreviation: $T_{½}$ = elimination half-life.

We found no major differences between cases and controls in the pattern of use of first-generation high-, intermediate-, and low-potency antipsychotic agents (high-potency: 11% vs 9%; intermediate-potency: 23% vs 24%; low-potency: 30% vs 25%) or second-generation antipsychotic agents (64% vs 63%).

The results of both the crude and adjusted conditional logistic regression analyses are presented in Table 2. The crude estimates for antipsychotic agents showed a tendency toward increased mortality with an increasing number of antipsychotics, but this tendency did not persist when adjusting for the variables in the final model.

The number of somatic comedications was clearly associated with gradually increasing mortality, which persisted in the multivariate model with an up to 27-fold increased risk. Current use of benzodiazepine derivatives was associated with increased mortality. When we included benzodiazepine categories according to their $T_{½}$ into the model, we found that the increased mortality was accounted for by benzodiazepines with long $T_{½}$, whereas the estimates were insignificant for intermediate and short $T_{½}$.

Age was not a major effect-measure modifier for the ratio effects of antipsychotic polypharmacy or current use

Table 2. Odds Ratio (OR) of the Association Between Mortality From Natural Causes and Medication

	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Number of concomitant antipsychotic drugs versus 1 (monotherapy)		
0	1.17 (0.74–1.87)	1.48 (0.89–2.46)
2	1.24 (0.86–1.77)	0.91 (0.61–1.36)
≥ 3	1.95 (1.21–3.14)	1.16 (0.68–2.00)
Current use of benzodiazepine derivatives and related drugs versus nonuse		
Long $T_{½}$ (> 24 h)	2.74 (2.01–3.72)	1.78 (1.25–2.52)
Intermediate $T_{½}$ (6–24 h)	1.02 (0.69–1.50)	0.75 (0.49–1.15)
Short $T_{½}$ (< 6 h)	1.32 (0.91–1.93)	1.16 (0.77–1.76)
Number of somatic comedications versus none		
1	1.34 (0.78–2.28)	1.36 (0.79–2.34)
2–4	1.96 (1.21–3.18)	1.89 (1.14–3.12)
5–9	8.21 (5.05–13.33)	7.49 (4.47–12.54)
≥ 10	28.85 (13.79–60.38)	26.94 (12.21–59.42)

[a]Adjusted for covariates in the final model (all antipsychotic and somatic comedication categories, epilepsy, and benzodiazepines).
Abbreviations: OR = odds ratio, $T_{½}$ = elimination half-life.

Table 3. Adjusted Odds Ratio (OR) of the Association Between Mortality From Natural Causes and Medication, Stratified by Sex

	Adjusted[a] OR (95% CI)	
	Men	Women
Number of concomitant antipsychotic drugs versus 1 (monotherapy)		
0	1.38 (0.73–2.61)	1.67 (0.70–3.96)
2	0.91 (0.55–1.50)	1.00 (0.49–2.02)
≥ 3	1.62 (0.85–3.09)	0.64 (0.23–1.77)
Current use of benzodiazepine derivatives and related drugs versus nonuse		
Long $T_{½}$ (> 24 h)	1.84 (1.20–2.82)	1.68 (0.90–3.13)
Intermediate $T_{½}$ (6–24 h)	0.65 (0.37–1.14)	0.91 (0.48–1.74)
Short $T_{½}$ (< 6 h)	1.37 (0.82–2.29)	0.87 (0.43–1.77)

[a]Adjusted for covariates in the final model (all antipsychotic and somatic comedication categories, epilepsy, and benzodiazepines).
Abbreviations: OR = odds ratio, $T_{½}$ = elimination half-life.

of benzodiazepines (data not shown). When stratifying by sex, we found a tendency to decreased risk of death with increasing number of antipsychotics in women, whereas men had an increased risk of death (Table 3). None of these estimates reached statistical significance. Sex was not an effect-measure modifier of the association between benzodiazepines and mortality.

DISCUSSION

Antipsychotic Polypharmacy

The literature on mortality and its possible association with antipsychotic polypharmacy remains inconclusive.[7] Our finding of no considerably increased risk of natural death in schizophrenia patients associated with antipsychotic polypharmacy is in line with some previous reports,[16,17] but contradictive findings have been reported by others. Joukamaa et al[18] reported a 2.50-fold (95% CI, 1.46–4.30) increased risk of natural death per antipsychotic agent added to the treatment regimen, Waddington and coworkers[19] found that the maximum number of antipsychotics given concurrently was associated with an increased risk of natural death (relative risk = 2.46; 95% CI, 1.10–5.47), and Hollis and colleagues[20] reported an increased risk of all cause mortality in patients receiving antipsychotic polypharmacy (OR = 5.32; 95% CI, 3.49–8.10).

A difficulty in comparing these studies with our findings and in general springs from the differences between the study populations (inpatients and outpatients, younger and elderly), different exposures (first- vs second-generation agents) and outcome measures (all cause vs only natural deaths), and partly from missing adjustment for somatic comorbidity and substance abuse.

We found sex to be an effect-measure modifier for the ratio effect, but the significance of this finding is difficult to interpret in terms of clinical recommendations. The results point to a protective effect in women prescribed antipsychotic polypharmacy, but this finding is highly unexpected.

Antipsychotic and Benzodiazepine Combination Therapy

We found a statistical association between concomitant use of antipsychotic agents and benzodiazepines with long $T_{½}$ and increased mortality. This is a worrying finding, but further research is necessary before any conclusions may be drawn regarding any causal role of benzodiazepines. It is advisable, though, to be cautious when prescribing this combination because of the very scarce evidence for the merit of benzodiazepines in schizophrenia. Studies of benzodiazepine augmentation of first-generation antipsychotics have generally not been able to show an effect, except in the management of psychiatric emergencies.[21,22] No published studies reliably address efficacy, tolerability, and safety of benzodiazepine augmentation of second-generation antipsychotics. Despite the missing evidence, benzodiazepines are extensively used, represented by nearly every second control in this study.

Somatic Comedications

The number of prescription drugs is a recognized comorbidity score,[23] and it was, therefore, expected that the number of somatic comedications would be associated with increased mortality. Only 16% of cases and 35% of controls received no somatic comedications, which suggests a substantial degree of somatic comorbidity. An even higher level of somatic comorbidity cannot be ruled out, since somatic illness is often unrecognized and untreated in patients with schizophrenia.[24]

Strengths and Limitations

The registers used in this study cover the entire Danish population, and the study, therefore, enjoys the strength of including all patients with schizophrenia fulfilling the inclusion criteria. These register qualities eliminate the

possibility of selection bias. The central Danish registers used are known to be of high quality, and they are widely used in register-based research.[11,12] Furthermore, this study is relatively large, as opposed to existing cohort counterparts, which affords it with a high statistical power. Owing to the complete registration of all filled prescriptions, it was possible to assess the entire drug use pattern for all subjects and to determine drug exposure immediately prior to death. We, thereby, avoided recall bias. We excluded unnatural deaths and unknown manner of death, thus eliminating suicide as a potential confounder.

There are several limitations to this study. It was not possible to fully control for confounding by indication, but we tried to minimize this potential bias by selecting a homogenous study population of outpatients with schizophrenia. We were unable to adjust for lifestyle factors, which are known potential risk factors regarding mortality in schizophrenia,[25] because these data were not available from the registers used in this study. It is plausible that antipsychotic and benzodiazepine (especially with long $T_{½}$) combination therapy is a marker of a vulnerable group of patients with more severe mental dysfunctions and, therefore, more pronounced disadvantageous lifestyle factors. Furthermore, it cannot be ruled out that the observed association between benzodiazepines with long $T_{½}$ and increased mortality was confounded by unregistered substance abuse, which is frequently undiagnosed in psychiatric patients.[26]

It should be noted that there is a potential for misclassification, since sequential trials of monotherapy with different antipsychotic agents could be classified as antipsychotic polypharmacy if they occurred within the 90-day period before the date of death or the index date. We tried to diminish this potential misclassification by excluding newly diagnosed patients, since this group is especially prone to switch antipsychotic agents. Furthermore, we manually reviewed the prescription history of all cases with regard to misclassification of combination therapy with 2 antipsychotics and found a possible misclassification in immediate relation to death in only a few (2) cases. However, even if a patient is switched from monotherapy with 1 antipsychotic agent to monotherapy with another antipsychotic agent, there will usually be a period of concomitant drug use (cross-titration) to avoid withdrawal symptoms and to ensure an adequate plasma level of the added drug before the former drug is discontinued. Thus, we do not believe that our results were substantially distorted by this potential misclassification bias.

It has recently been shown that record linkage studies using computerized health care databases and not considering hospitalizations occurring during the observation period are prone to a particular type of bias, labeled immeasurable time bias.[27] Exposure during a period of hospitalization is immeasurable because no outpatient prescriptions can be obtained during this time. During the 90 days prior to death or the index date, 20 of our 193 cases and 147 of our 1,937 controls were hospitalized. The majority of these cases were hospitalized for less than 20 days, whereas the controls were hospitalized for up to 75 days. When restricting the analysis to subjects who were not hospitalized in the 90-day exposure period prior to death or the index date, our risk estimates did not change considerably, which testifies to the limited importance of this potential confounder in our study (data not shown).

Another important limitation was that we were unable to assess the cause of death, which would have shed further light on the association under interest. Proposed mechanisms for possible adverse effects with fatal outcome in antipsychotic drug users include prolongation of the QT_c-interval, toxic cardiomyopathy, cardiac arrhythmias, vascular collapse, hyperpyrexia, extrapyramidal side effects (laryngeal-pharyngeal dystonia, aspiration, asphyxia), anticholinergic side effects (ileus, urinary retention, pyelonephritis), diabetes mellitus, and deep venous thrombosis with pulmonary embolism.[28,29] Additionally, we were unable to evaluate single drug combinations due to the high variability of combinations of different antipsychotics taken concomitantly.

With the high degree of somatic comedications taken into consideration, it is also possible that some of the deaths were related to drug-drug interactions with a fatal outcome. However, our study did not have the power to detect outcomes of potential drug-drug interactions due to infrequent prescribing of the individual drug combinations. Potential pharmacokinetic drug-drug interactions, which should be avoided and are, therefore, of possible clinical relevance, were checked in the Danish national drug interaction database.[30] Only a negligible number of interactions were identified and were, therefore, not relevant to the conclusions of this study. We did not assess potential drug-drug interactions that can be managed by dose adjustment, because dosage information is generally not documented in the prescription database. Moreover, it is of importance to note that all documented drug-drug interactions only refer to combinations of pairs of drugs, while most of our cases received a cocktail of many drugs.

Antipsychotic polypharmacy did not contribute to the excess mortality from natural causes in middle-aged patients with schizophrenia. However, there is no reason to question the relevance of current recommendations to primarily employ antipsychotic monotherapy in the absence of evidence of the value of polypharmacy. We can only be comforted that this widespread practice fortunately does not seem to shorten the life span of our patients in this observational study. The detected increased risk of death associated with benzodiazepines with long elimination half-lives calls for further clarification.

Drug names: alprazolam (Xanax, Niravam, and others), chlordiazepoxide (Limbitrol, Librium, and others), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), diazepam (Diastat, Valium, and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), methadone (Methadose, Dolophine, and others), triazolam (Halcion and others), zolpidem (Ambien, Edluar, and others), zopiclone (Lunesta).

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