Exploring Regional Variation in Antipsychotic Coprescribing Practice: A Danish Questionnaire Survey

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Objective: The pharmacologic treatment of schizophrenia is characterized by excessive use of antipsychotic polypharmacy, which reflects a gap between evidence and practice. The aim of the present study was to investigate regional differences in treatment setting characteristics and in physician and nurse attitudes toward antipsychotic polypharmacy and clinical guidelines.

Method: Cross-sectional postal questionnaire survey directed to physicians and nurses at 2 pairs of treatment settings in Denmark, characterized by low and high prevalence of antipsychotic polypharmacy, respectively. The questionnaire investigation was conducted during November 2007 to February 2008.

Results: Satisfactory response rates were obtained (physicians: 93%; nurses: 87%). The treatment settings with low use of antipsychotic polypharmacy were characterized by raised knowledge/awareness of local antipsychotic treatment guidelines ($P = .02$ for physicians; $P = .01$ for nurses). Among physicians, these settings were also characterized by an elevated confidence in these guidelines ($P = .01$), frequent local educational activities ($P < .0001$), and increased recent involvement in research ($P = .01$). Among nurses, a perception of an overwhelming work load ($P = .01$) and time pressure ($P = .003$) was significantly more prevalent in treatment settings with high rates of antipsychotic coprescribing, as was the belief in the benefit of antipsychotic polypharmacy augmentation ($P = .001$).

Conclusion: Albeit no causal relationships can be inferred from this cross-sectional observational study, we recommend the furtherance of a treatment environment characterized by easily accessible clinical guidelines, frequent academic activities, and an unruffled atmosphere.

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Concomitant prescription of more than one antipsychotic agent (antipsychotic polypharmacy) is not a novel concept. This controversial treatment regimen has been debated since the introduction of the first-generation antipsychotics in the 1950s.[1] The debate gained new momentum with the advent of the second-generation antipsychotics, because potentially beneficial combinations have been suggested on the basis of the different receptor profiles alone. The recent rise in antipsychotic polypharmacy, with prevalence rates reaching some 50%,[2–5] has fueled a growing concern because evidence of the superior efficacy of polypharmacy compared with antipsychotic monotherapy is lacking.[6–9] Moreover, it has been indicated that the main advantage of the second-generation antipsychotics, ie, their tendency to induce fewer and less severe side effects associated with dopamine D_2 receptor blockade (extrapyramidal side effects and hyperprolactinemia),[10] is neutralized when they are being combined with first-generation agents.[5,10,11] Furthermore, antipsychotic coprescribing is strongly associated with increased total dose of antipsychotic medication[12–14] and, as such, with an increased rate of side effects.[14] Antipsychotic polypharmacy also augments the general disadvantages of polypharmacy, including reduced compliance,[15] increased risk of pharmacokinetic and pharmacodynamic interactions,[16] medication errors,[15] and increased costs.[3,17,18]

Reflecting this array of potential disadvantages and the very few potential benefits, the various antipsychotic treatment guidelines for schizophrenia[19–23] recommend several sequential trials of antipsychotic monotherapy, including clozapine, before progressing to antipsychotic polypharmacy. Thus, there is a wide gap between recommended treatment regimens and actual care, and explanations for the high prevalence of antipsychotic polypharmacy despite recommendations of the opposite are still broadly lacking. The most common reasons for antipsychotic coprescribing stated by psychiatrists include a wish to (1) reduce positive and negative symptoms, (2) decrease the total amount of medication, and (3) reduce extrapyramidal side effects.[24,25] Despite these cited reasons for combining antipsychotics, psychiatrists do not perceive this treatment strategy to be particularly effective in reducing psychotic symptoms, improving overall functioning, or reducing rehospitalization.[26]

Regional Variation in Prescribing Patterns

The lack of adherence to evidence-based treatment guidelines is matched by much discrepancy between countries and across hospitals in prescription patterns, including prescription of antipsychotic polypharmacy.[27–29] It has recently been suggested that the regional variation in prescribing habits could be used to identify which factors drive this variation and thus to gain insight into why guidelines are readily implemented in some treatment settings, but not in others.[30]

The Prescribing Process

Psychiatric drug prescribing has been described by Benson[31] as a sequential decision-making process that involves physician-, patient-, and treatment-setting characteristics. Hemminki,[32] who mainly reviewed the field of general practitioners, discussed how the following factors

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affect drug prescribing in general: education, advertising (underlining the role of the drug industry), colleagues, control and regulation measures, demands from society and patients, and doctor characteristics. Cabana et al[33] extensively reviewed barriers to physician adherence to clinical guidelines and created a framework consisting of barriers affecting physician knowledge, attitudes, and behavior. We used elements from these frames to develop a questionnaire to be distributed among physicians and nurses at treatment settings with varying prevalence of antipsychotic polypharmacy.

The Aim of the Study

The aim of the present study was to investigate regional differences in treatment setting characteristics and in physician and nurse attitudes toward antipsychotic polypharmacy and clinical guidelines. It was hypothesized that settings with increased antipsychotic coprescribing frequency were associated with the following structures:

Knowledge and attitudes:
- Less accessibility and awareness of antipsychotic treatment guidelines, less frequent use of and more negative attitudes toward these
- More positive perception of antipsychotic polypharmacy

Treatment setting characteristics:
- Fewer local educational activities, less course and conference attendance
- Less research activity
- Higher perceived work load

Behavioral characteristics:
- Lower frequency of scientific reading
- Shorter tenure in psychiatry

METHOD

Selection of Inclusion Settings

In collaboration with the Danish National Board of Health and the Danish Medicines Agency, register linkage data from 2004 was used to determine the prevalence of antipsychotic polypharmacy in each municipality in Denmark. For this purpose, antipsychotic polypharmacy was defined as the filling of prescriptions for more than one antipsychotic agent within 30 days during the calendar year 2004. For each of the 98 municipalities (according to the 2007 reform), we determined the number of outpatients with diagnoses of schizophrenia spectrum disorders (*International Classification of Diseases, 10th Revision*: F20–F29), 18–64 years of age, and treated with antipsychotic polypharmacy compared with the total number of antipsychotic-treated schizophrenia spectrum patients. This ratio was termed the *APP fraction*. The national mean was 48.5%, and all municipalities with an APP fraction above and below this mean were further evaluated. Finally, 4 municipalities were chosen: 2 with low and 2 with high APP fractions compared with the national mean. Two municipalities from each of these categories were chosen in order to increase the study population size. Inclusion criteria: An effort was made both within and between the pairs to select municipalities with comparable need for mental health services determined by a priori selected socioeconomic variables known to predict the need for mental health services in a certain region.[34] It was also essential that the eligible municipalities had a balanced organization of the psychiatric treatment system in which the outpatient services were located in the same municipality as the inpatient services. Furthermore, the catchment areas had to be of a certain size to ensure a sufficient number of employed physicians. The only combinations of municipalities fulfilling these requirements were

Settings with a low APP fraction:
- Frederiksberg (92,234 inhabitants [as of January 1, 2007],[35] inner city catchment area) and
- Odense (including Kerteminde and Nyborg with a total of 241,777 inhabitants,[35] provincial town catchment area).

Settings with a high APP fraction:
- Esbjerg (114,148 inhabitants,[35] provincial town catchment area) and
- Viborg (91,405 inhabitants,[35] provincial town catchment area).

Frederiksberg is situated in the middle of the capital (Copenhagen). The other 3 municipalities are all located well outside the capital region. Frederiksberg is usually known as a high-income and wealthy area, but analysis of socioeconomic variables showed homogeneity between the municipalities, except that Frederiksberg tended to be more, not less, burdened compared with Odense, Esbjerg, and Viborg, reflecting a metropolitan effect (data not shown). All the treatment settings in the selected municipalities agreed to participate.

This classification into low- and high-prevalence regions was based on 2004 register linkage data because of the inevitable time lag associated with register data. To verify that these APP fractions still applied when the questionnaire investigation was conducted during November 2007 to February 2008, we (1) obtained access to an updated 2007–2008 register linkage survey when these data became available in January 2009 and (2) manually registered the APP fractions of the actual outpatients (cross-sectional status as of January 1, 2008) in the selected regions. Table 1 shows that the manually calculated APP fraction was higher than would be expected from the 2004 register data in the 2 high-prevalence regions, but it was also somewhat higher in Frederiksberg, one of the low-prevalence regions. Because the APP fraction in Frederiksberg was higher than expected (but still below the national mean and as such still classified as a low-prevalence region), it was decided to include a sensitivity analysis with only Odense as a low-prevalence region and with Frederiksberg excluded. The 2004 frequencies were grossly replicated in the updated 2007–2008 register linkage data, indicating that the APP fraction in our inclusion settings had remained stable since 2004. As expected, the manually calculated APP fractions were generally a bit higher than the corresponding 2007–2008 register linkage data (based on filled prescriptions) due to noncompliance.

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Table 1. APP Fraction in the Inclusion Areas[a]

Inclusion Areas	2004[b]	January 1, 2008[c]	2007–2008[d]
Frederiksberg	35%	45% (37%–53%)	47%
Odense	41%	38% (30%–46%)	44%
Esbjerg	59%	69%	58%
Viborg	61%	66%	60%

[a]APP fraction: the ratio of the number of outpatients with diagnoses of ICD-10 schizophrenia spectrum disorders, 18–64 years of age, and treated with antipsychotic polypharmacy to the total number of antipsychotic-treated schizophrenia spectrum patients.
[b]Register linkage data: antipsychotic polypharmacy was defined as filling of prescriptions for more than 1 antipsychotic agent within 30 days during the calendar year 2004 (national mean: 48.5%).
[c]Cross-sectional manual count of prescribed antipsychotics: Frederiksberg and Odense, samples of 150 outpatients each (95% confidence intervals in parentheses); Esbjerg and Viborg, all outpatients included.
[d]Register linkage data: antipsychotic polypharmacy was defined as filling of prescriptions for more than 1 antipsychotic agent within 30 days during the year from July 1, 2007, to June 30, 2008 (national mean: 46.0%).

To demonstrate that the different APP fractions were not attributable to differences in disease severity, we used register data from The Danish National Indicator Project (NIP), which measures the quality of care provided by the health care system across a range of medical conditions, in casu, schizophrenia. From this NIP database, we extracted the Global Assessment of Functioning (GAF) scores and substance abuse data for the schizophrenia patients in the 4 chosen geographical regions.

The Questionnaires

In the absence of an appropriate existing questionnaire, we designed a questionnaire for this particular purpose, following basic recommendations for questionnaire design.[36–39] It was hypothesized that both physicians' and nurses' knowledge and attitudes affected antipsychotic polypharmacy prescribing practices.[40,41] We therefore designed questionnaires for these 2 groups that were basically identical, but differed where cognitive interviews had indicated that differences were appropriate. Topics were defined and questions formulated to explore the study hypotheses, and extra information was obtained to be able to describe demographic variables. To confirm face validity, the questionnaire was presented to a group of consultant psychiatrists who also had research experience. The questionnaires were tested in 3 cognitive interviewing rounds[42] with 5 subjects in each round. Physicians and nurses engaged in one of the main psychiatric departments in the capital region served as test subjects and as such belonged to the target population. The cognitive interviewing technique applied was primarily think-aloud, but elements from verbal probing were also utilized.[42] The questions were rephrased and response categories optimized to make them comply with the results of the interviews. Cognitive interviewing has been developed to minimize problems involving the comprehension, recall, decision, and response processes necessary to adequately answer a questionnaire, and in our study the process served to confirm the content validity of the questionnaire.

For attitude questions, we used a Likert scale with 4 response categories ranging from "strongly agree" to "strongly disagree." This was supplemented by a neutral response category when required according to interview feedback. The remaining questions were supplied with a sufficient number of response categories to ensure that they would cover possible respondent answers. It was aimed to use short sentences, simple and direct language, and to provide variation (both open and closed questions, mix of positively and negatively phrased statements) to maintain the respondents' interest. The open-ended questions concerned partly numerical variables, partly the subject of courses, and research in which analytic categories were chosen a priori (related to psychopharmacology or not). Consequently, quantitative analysis methods were not applied. In order to keep the questionnaire at a reasonable length (and thereby increase the chance of satisfactory response rates), we did not explicitly address all of the proposed issues in the aforementioned theoretical framework,[31–33] but selected those that seemed most relevant in our context. A copy of the questionnaire is available on request.

Sample sizes were estimated according to testing hypotheses for differences between 2 population proportions, as described by Lwanga and Lemeshow.[43] Using the first item as an example, we judged it clinically important to be able to identify a difference of minimum 35% between the proportions (in the low- and high-prevalence settings, respectively) agreeing on that item. Demanding a power of 80% and a significance level of .02, this yielded a sample size of 32 in each group of physicians and nurses in each of the combined prevalence groups (a total of 64).

The Survey

The questionnaire was distributed to all physicians and nurses in the psychiatric departments and outpatient clinics servicing inhabitants in the selected municipalities. Sections only involved in the treatment of the elderly were excluded. None of the nurses in the study were authorized to prescribe medication. We did not include psychiatrists working in private clinics because they are treating only a negligible fraction of the patients with schizophrenia in Denmark.

The participants received a cover letter, the questionnaire, and a stamped reply envelope. Questionnaires were sent out according to the following scheme in which each subsequent step was only taken toward nonrespondents to the previous step: electronic form when e-mail addresses were available, electronic reminder after 1 week, postal questionnaire after 2 more weeks, postal reminder after 2 more weeks, and a telephone reminder after 1 more week.

To further encourage participation, we introduced an economic incentive in the form of a gift token to a respondent (in each of the 4 regions) chosen by lot. Anonymized data were entered into a database independently by 2 persons (L.B. being one of them in each case).

Categorical variables were evaluated using χ^2 test (or Fisher exact test when expected cell values fell below 5) and continuous variables using nonparametric Wilcoxon test to

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Table 2. Response Rates

	Regions With Low APP Fraction				Regions With High APP Fraction					
	Frederiksberg		Odense		Esbjerg		Viborg		Total	
Group	n/n	%	n/n	%	n/n	%	n/n	%	n/n	%
Physicians	17/19	89	29/31	94	15/17	88	17/17	100	78/84	93
Nurses	45/51	88	72/88	82	54/60	90	59/64	92	230/263	87
Total	62/70	89	101/119	85	69/77	90	76/81	94	308/347	89

Table 3. Demographics of Respondent Physicians

Physician Characteristics	Regions With Low APP Fraction, n = 46[a]	Regions With High APP Fraction, n = 32[a]	Test Statistic
Age, n (%)			$P = .86$[b]
< 30 y	1 (2)	1 (3)	
30–39 y	8 (17)	9 (31)	
40–49 y	17 (37)	8 (28)	
50–59 y	14 (30)	5 (17)	
≥ 60 y	6 (13)	6 (20)	
Gender, n (%)			$P = .97$[c]
Men	21 (46)	14 (45)	
Women	25 (54)	17 (55)	
Position, n (%)			$P = .19$[c]
Resident	19 (41)	17 (57)	
Specialist	27 (59)	13 (43)	
Staff turnover since 2004, n (%)	22 (48)	18 (58)	$P = .38$[c]

[a]Not all respondents answered all questions (1%–4% missing data in these items).
[b]Nonparametric Wilcoxon test.
[c]χ^2 test.

investigate if there was any association between the variables and the 2 combined antipsychotic polypharmacy prevalence regions. The response categories to each question were dichotomized before statistical analysis in order to simplify the interpretation. The response categories for the attitude questions were dichotomized into "agree" ("strongly agree" and "agree" combined) and "disagree" ("disagree" and "strongly disagree" combined). The analysis focused on affirmative answers ("agree"), and the neutral response was pooled with the negative answers ("disagree"). For the remaining questions, the response categories were dichotomized a priori into natural and clinically relevant categories. To correct for multiple testing, we used an a priori–defined significance level of .02 (further discussed in the Strengths and Limitations section below). For the questions that reached this level of statistical significance, an odds ratio (OR) was also calculated followed by a 98% confidence interval (CI).

To compare administrative variables among the settings, supplementary data from the individual treatment settings in the inclusion areas were collected: proportion of occupied beds (data available from the National Board of Health[44]), research activity, number of academic staff, existence/accessibility of a local antipsychotic treatment guideline (as perceived by the head of the department), when it was last updated, and initiatives to encourage adherence to such a guideline.

The study was approved by the regional research ethics committee of the capital region and the Danish Data Protection Agency.

Table 4. Demographics of Respondent Nurses

Nurse Characteristics	Regions With Low APP Fraction, n = 117[a]	Regions With High APP Fraction, n = 113[a]	Test Statistic
Age, n (%)			$P = .25$[b]
< 30 y	15 (13)	18 (16)	
30–39 y	28 (25)	36 (33)	
40–49 y	35 (31)	21 (19)	
50–59 y	30 (27)	24 (22)	
≥ 60 y	5 (4)	11 (10)	
Gender, n (%)			$P = .77$[c]
Men	14 (12)	15 (13)	
Women	103 (88)	98 (87)	
Position, n (%)			$P = .72$[c]
Basic nurse	98 (84)	95 (84)	
Clinical nurse specialist	5 (4)	7 (6)	
Leading nurse	14 (12)	11 (10)	
Staff turnover since 2004, n (%)	56 (49)	51 (46)	$P = .68$[c]

[a]Not all respondents answered all questions (1%–4% missing data in these items).
[b]Nonparametric Wilcoxon test.
[c]χ^2 test.

Table 5. Data From the NIP Database Reflecting the Functional Level of the Patients in the Inclusion Areas

Patient Characteristics,[a] 2007	Regions With Low APP Fraction, n = 1,247	Regions With High APP Fraction, n = 823
GAF score, mean (SD)	40.8 (10.7)	37.6 (8.4)
Substance abuse type, n (%)		
Alcohol	285 (23)	191 (23)
Cannabis	173 (14)	127 (15)
Benzodiazepine	53 (4)	80 (10)
Central stimulants	45 (4)	83 (10)

[a]Both outpatients and inpatients.
Abbreviations: GAF = Global Assessment of Functioning, NIP = The Danish National Indicator Project.

All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

A total of 78 physicians (93%) and 230 nurses (87%) responded to the questionnaire, giving an overall response rate of 89% (Table 2). Therefore no statistical analysis of nonrespondents was carried out. The analysis revealed that one of the questions about work load was ambiguous (despite our efforts to prevent this) and it was therefore excluded. Generally, the frequency of missing data (respondents not answering individual items) was between 0 and 6 percent with a few exceptions (see footnotes in Tables 3–7 for details).

The distribution of age, gender, position, and staff turnover was not significantly different between the low and high APP fraction settings (Tables 3 and 4).

To compare the functional level of the patient population in the low- and high-prevalence areas, data were extracted from the NIP database (covering > 90% of the schizophrenic population) and shown in Table 5. Although there was a statistically significant difference between the

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Table 6. Questionnaire for Physicians (condensed form), Answer in the Affirmative for Each Item Is Given

Subject of Item	Low,[a,b] n = 46, n (%)	High,[a,b] n = 32, n (%)	Test Statistic[c]	P[d]	OR[e] (98% CI)
Knowledge/awareness of local antipsychotic treatment guideline	40 (87)	20 (65)	$\chi^2 = 5.42$	.02	3.67 (0.96–14.03)
Frequency of use of antipsychotic treatment guideline at least every week	21 (48)	14 (45)	$\chi^2 = 0.05$	.83	
Whether it is important to follow an antipsychotic treatment guideline	43 (96)	26 (84)	Fisher exact test	.11	
Whether antipsychotic treatment guidelines are simple to follow	38 (84)	30 (97)	Fisher exact test	.13	
Whether antipsychotic treatment guidelines ignore the individual needs of a patient	12 (26)	10 (32)	$\chi^2 = 0.35$	.56	
Whether personal experience is more important than antipsychotic treatment guidelines when prescribing antipsychotics	6 (13)	12(38)	$\chi^2 = 6.10$	.01	0.26 (0.07–0.97)
Whether antipsychotic polypharmacy is useful in order to increase effect	2 (4)	4 (13)	Fisher exact test	.22	
Whether antipsychotic polypharmacy is useful in order to reduce side effects	5 (11)	2 (6)	Fisher exact test	.69	
Local education for physicians offered twice a week	35 (76)	3 (9)	$\chi^2 = 33.62$	< .0001	30.76 (6.06–156.04)
Participation in local education for physicians twice a week	6 (13)	1 (3)	Fisher exact test	.23	
Attendance to courses and conferences (≤ 10 days) during the past year	23 (50)	19 (61)	$\chi^2 = 0.95$	.33	
Salaries received during attendance to courses and conferences (all days)	40 (87)	28 (90)	Fisher exact test	.67	
Subject of courses and conferences related to psychopharmacology[f]	20 (54)	10 (38)	$\chi^2 = 1.49$	.22	
Course participation funded by pharmaceutical company	28 (62)	15 (47)	$\chi^2 = 1.79$	.18	
Perception of sufficient time for each patient	19 (41)	10 (31)	$\chi^2 = 0.82$	.37	
Perception of too high work load	18 (39)	18 (58)	$\chi^2 = 2.67$	.10	
Research activity[g] during the past 3 years	19 (41)	4 (13)	$\chi^2 = 6.73$	.01	4.57 (1.09–19.12)
Whether research activity was related to psychopharmacology[h]	3 (7)	2 (7)	Fisher exact test	1.00	
Frequency of scientific reading at least once a week	32 (70)	27(87)	$\chi^2 = 3.18$	.07	
Length of experience in psychiatry (< 5 years)	17 (37)	13 (42)	$\chi^2 = 0.19$	.66	

[a]Settings with respectively low and high APP fraction.
[b]Not all respondents answered all questions (0%–4% missing data with exceptions mentioned below).
[c]All χ^2 tests with 1 degree of freedom.
[d]Significant at $P < .02$.
[e]An OR > 1 indicates that the low antipsychotic polypharmacy prevalence regions had more confirmative answers.
[f]19% missing data.
[g]Defined as poster/oral presentation at scientific meeting, first author or coauthor of article published in peer-reviewed journal, or research position.
[h]9% missing data.

Table 7. Questionnaire for Nurses (condensed form), Answer in the Affirmative for Each Item Is Given

Subject of Item	Low,[a,b] n = 117, n (%)	High,[a,b] n = 113, n (%)	Test Statistic,[c] χ^2	P[d]	OR[e] (98% CI)
Knowledge/awareness of local antipsychotic treatment guideline	86 (74)	64 (58)	6.87	.01	2.11 (1.08–4.10)
Frequency of use of antipsychotic treatment guideline at least every week	14 (12)	25 (23)	4.49	.03	
Whether antipsychotic treatment guidelines are simple to follow	73 (63)	61 (56)	1.31	.25	
Whether antipsychotic treatment guidelines ignore the individual needs of a patient	25 (22)	19 (18)	0.66	.42	
Whether antipsychotic polypharmacy is useful in order to increase effect	21 (19)	41 (38)	10.57	.001	0.37 (0.18–0.76)
Whether antipsychotic polypharmacy is useful in order to reduce side effects	21 (19)	18 (17)	0.12	.73	
Local education for nurses offered at least once a month	39 (34)	56 (50)	5.99	.01	0.52 (0.27–0.97)
Participation in local education for nurses at least once a month	30 (27)	41 (37)	2.63	.10	
Attendance to courses and conferences (≤ 5 days) during the past year	67 (61)	75 (72)	2.72	.10	
Salaries received during attendance to courses and conferences (all days)	107 (94)	105 (96)	0.73	.39	
Subject of courses and conferences related to psychopharmacology	31 (27)	22 (20)	1.70	.19	
Course participation funded by pharmaceutical company	28 (24)	35 (31)	1.44	.23	
Perception of sufficient time for each patient	64 (57)	40 (37)	8.92	.003	2.27 (1.19–4.31)
Perception of too high work load	29 (26)	47 (44)	7.31	.01	0.46 (0.23–0.90)
Research experience	35 (30)	30 (27)	0.32	.57	
Whether research activity was related to psychopharmacology[f]	14 (13)	8 (8)	1.20	.27	
Frequency of scientific reading at least once a week	49 (42)	58 (52)	2.26	.13	
Length of experience in psychiatry (< 5 years)	28 (24)	37 (33)	2.20	.14	

[a]Settings with respectively low and high APP fraction.
[b]Not all respondents answered all questions (1%–6% missing data with exception mentioned below).
[c]All χ^2 tests with 1 degree of freedom.
[d]Significant at $P < .02$.
[e]An OR > 1 indicates that the low antipsychotic prevalence regions had more confirmative answers.
[f]9% missing data.

patient populations in terms of GAF scores and abuse of benzodiazepines and central stimulants (lower and higher in high-prevalence areas, respectively), the differences seemed of minor relevance from a clinical point of view.

The items of the questionnaires are shown in condensed form in the left column of Tables 6 and 7.

For physicians, the following structures revealed significant differences between the low- and high-prevalence treatment settings (Table 6):

Raised knowledge/awareness of local antipsychotic treatment guideline in settings with a low APP fraction as compared with settings with a high APP

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fraction (OR = 3.67, *P* = .02). This difference was just at the level of our a priori–defined significance level, but it was confirmed in the sensitivity analysis, in which a *P* value of .002 (OR = 15.40) was found. The OR indicates the odds of being aware of local antipsychotic treatment guideline in low- compared with high-prevalence treatment settings.

- Physicians in low APP fraction settings believed less in the value of personal experience than in antipsychotic treatment guidelines (OR = 0.26, *P* = .01, sensitivity analysis: OR = 0.13, *P* = .01).
- Physicians in low-prevalence regions were offered local educational sessions more often than their high-prevalence counterparts (OR = 30.76, *P* < .0001, same *P* value in sensitivity analysis), but we found no statistically significant differences in the frequency of attendance to these educational activities.
- Physicians in low-prevalence regions were more engaged in recent scientific activity than physicians in high-prevalence regions (OR = 4.57, *P* = .01, sensitivity analysis: OR = 4.59, *P* = .02).

For nurses, the following structures revealed significant differences between the low- and high-prevalence treatment settings (Table 7):

- Raised knowledge/awareness of local antipsychotic treatment guideline in settings with a low prevalence of antipsychotic polypharmacy as compared with settings with a high prevalence (OR = 2.11, *P* = .01, sensitivity analysis: OR = 5.82, *P* < .0001).
- Significantly fewer nurses in low-prevalence regions were convinced that antipsychotic polypharmacy was a useful means for increasing the effect of antipsychotic treatment (OR = 0.37, *P* = .001, sensitivity analysis: OR = 0.41, *P* = .01).
- Nurses in low-prevalence regions were offered local educational activities less often than their high-prevalence counterparts (OR = 0.52, *P* = .01), which was contrary to our expectations, but this association did not persist in the sensitivity analysis and was therefore considered weak.
- Significantly more nurses in low-prevalence regions than in high prevalence-regions found that they had sufficient time for each patient (OR = 2.27, *P* = .003, sensitivity analysis: OR = 2.29, *P* = .01).
- Nurses in the former regions also felt less burdened by the work load than nurses in the latter (OR = 0.46, *P* = .01, sensitivity analysis: OR = 0.39, *P* = .01). This tendency to increased time pressure in the high-prevalence settings was also found for the physicians, but differences in this group did not reach statistical significance.

Research activity as determined by the number of published articles in peer-reviewed journals in 2006 ranged from 8 to 11 in the low APP fraction settings and 0 to 1 in the high APP fraction settings. Regarding the number of academic staff, only Odense stood out, having 7 associate professors (1 in Frederiksberg, 0 in Esbjerg, and 1 in Viborg) and 1 professor (none in the other settings). The head of all participating treatment settings reported to have a local antipsychotic treatment guideline. The latest update was in June 2007 for the low-prevalence settings and 2004 and 2007 for the high-prevalence settings. All settings reported that they engaged in some form of activities to ensure implementation of the antipsychotic treatment guideline in the clinic (mostly discussions at conferences and audit) and systematic differences between low- and high-prevalence settings could not be distinguished from the answers. Using data from 2006 and 2007, we discovered that the proportion of occupied beds as a crude proxy of work pressure gave the following results: 94% and 100% for the 2 low-prevalence areas and 96% for both of the 2 high-prevalence areas. Thus, no systematic pattern could be distinguished.

DISCUSSION

This study addressed the regional variation in the frequency of antipsychotic coprescribing patterns and identified some structures, especially attitudinal and academic, characterizing the different treatment settings. Our findings are in line with previous reports that suggest an association between antipsychotic polypharmacy and the following factors: nurses' request (to increase the current dosage or add another drug)[41] and physician-related factors such as psychiatrists' knowledge and perception of medication, skepticism toward algorithms, and time pressure.[40,41,45]

The differences in perception of work load and time pressure were noticeable for both physicians and nurses, but were only statistically significant for nurses. We interpret this finding as a marker of a more harassed working environment in the high-prevalence settings where, perhaps, the time pressure could be part of the causal chain in antipsychotic polypharmacy prescribing.

It has previously been shown that nonteaching hospitals tend to prescribe polypharmacy more often than teaching hospitals[46]; however, the grounds for this have not yet been explored. Only the 2 low APP fraction settings were situated in university cities, but medical students were received in both low- and high-prevalence settings and both categories therefore had teaching responsibilities. It is possible that the distance to the nearest academic environment had some impact on the prescribing habits, but this impact was operating through some underlying factors, some of which may very well be those identified in this study. This is also reflected in the fact that the low-prevalence settings had published a total of 19 articles in peer-reviewed journals during 1 year compared with only 1 in the high-prevalence settings. Obviously, there is no direct link between the number of published articles and the frequency of antipsychotic coprescribing, but it may serve as a marker of an innovative and critical environment, in which new guidelines are more easily implemented.

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We found no differences in the frequency of attendance to educational activities sponsored by a pharmaceutical company and could therefore not support what others have found in this respect.[26] Although only covering one aspect of prescribing habits, we consider this finding important, because education offered by the pharmaceutical industry is often questioned ethically.

Strengths and Limitations

The satisfactory response rates across all settings indicate that our sample was highly representative of the staff in the selected settings, which is essential to a questionnaire survey. The persistency of the results as evidenced by the sensitivity analysis testifies to the robustness of the results.

It was not possible to assess the prescribing habits of the individual physicians participating in the questionnaire survey, and we therefore could not correlate the physician responses with the individual physicians' prescribing practices.

Likewise, we compared GAF score and substance abuse between the inclusion areas at a group level and could therefore not investigate any association with antipsychotic coprescribing frequency in individual patients. However, other studies investigating individual patient variables as predictors of antipsychotic polypharmacy have not found higher rates in substance abusers, whereas the data regarding disease severity are inconclusive.[28,47–49]

Apart from the demographic variables, another 20 items (18 for nurses) were tested for their association with antipsychotic coprescribing frequency. This gives rise to the statistical problem of multiple testing (increased risk of type I error when testing several hypotheses simultaneously), which may be corrected for by means of the Bonferroni method. However, precise determination of the Bonferroni-corrected significance level was complicated because of difficulties in determining the independency of the individual questionnaire items. Bonferroni correction is only required for independent tests, and using n = 20 would yield a much too conservative estimate (a *P* value of .05/20 = .003) because of the intertwined nature of the individual items. The items were grouped into 3 categories (knowledge and attitudes, treatment setting characteristics, and behavioral characteristics), and therefore it was judged reasonable to apply a significance level of .02 (.05/3).

Generally, the cross-sectional design of the study prohibits any causal inferences. Furthermore, because of its observational design, it is possible that the study groups differed with regard to important, but unmeasured variables that may have accounted for part of the differences in antipsychotic coprescribing.

Development of a new questionnaire is always a laborious task with many possible pitfalls.[37,38] The content validity was optimized by the cognitive interviewing process, which placed special emphasis on the phrasing of the first item to ensure that all possible respondents knew what the concept "antipsychotic treatment guideline" covered. Despite these efforts, it was evident (from stray handwritten notes next to the question on a few nurse questionnaires) that an unknown proportion of the nurses mistook the term for a general drug catalog (covering all drugs with regard to indication, recommended dosage, side effects, etc).

We did not test the reliability in a systematic test-retest paradigm before the study. However, 5 of the respondents answered the questionnaire twice because their first response and the reminder crossed in the mail. These 5 pairs of responses were evaluated to get an indication of the test-retest reliability of the questionnaire. The κ value for the questions on attitude (measured on the Likert scale) was computed, which resulted in a κ value of 0.88 corresponding to a very good strength of agreement.

The method applied for sample size calculation assumes random sampling, and because our respondents were sampled in clusters, there is a risk that the study is underpowered, especially with regard to physicians, which was the limiting category. This important limitation is also reflected in the much wider CIs for physicians than for nurses.

Albeit no causal relationships can be inferred from this cross-sectional observational study, we recommend the furtherance of a treatment environment characterized by easily accessible clinical guidelines, frequent academic activities, and an unruffled atmosphere. The identified structures appear so general and unrestricted to antipsychotic polypharmacy that high transferability to other domains in psychiatry is likely, but this remains to be proven.

Drug names: clozapine (Clozaril, FazaClo, and others).

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