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Neuroleptics and mortality in schizophrenia: prospective analysis of deaths in a French cohort of schizophrenic patients

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Abstract

Objective: The putative role of neuroleptics in the known excess mortality of subjects with schizophrenia remains disputed. The aim of this study was to assess the link between mortality and the class of neuroleptic. *Method*: Causes of death (suicide, cardiovascular, etc.) and exposure to neuroleptics were studied in a cohort of 3474 patients with schizophrenia followed from 1993 to 1997. *Results*: From 1993 to 1997, 178 patients died. The risk of all-cause death (OR = 1.59; 95% CI 1.02–2.50; $p = 0.04$), and suicide (OR = 2.22; 95% CI 1.24–3.97; $p = 0.006$) were increased in users of thioxanthenes (alone or associated with other drugs), and increased risk of "other causes" of death was associated with use of atypical neuroleptics (OR = 2.06; 95% CI 1.15–3.70; $p = 0.0016$). *Conclusion*: Our findings suggest the existence of association between certain classes of neuroleptics and death, all cause or specific. This could be related to the drug itself or to patient selection.

Keywords: Schizophrenia; Causes of death; Classes of neuroleptic; Thioxanthenes

1. Introduction

Mortality in patients with schizophrenia is 2 to 3 times higher than in the general population (Black and Fisher, 1992; Brown, 1997; Harris and Barraclough, 1998; Osby et al., 2000) and up to 10 times higher for suicide and accidents (Allebeck, 1989; Harris and Barraclough, 1997; Mortensen and Juel, 1990). Neuroleptics could be involved in this excess mortality in various ways: mis-swallowing and food inhalation leading to asphyxia or respiratory disorders, intestinal paralysis or obstruction (Mortensen and Juel, 1990), sudden death because of laryngeal spasm (Modestin et al., 1981) or arrhythmia (Adamantidis et al., 1994; Appleby et al., 2000; Drici et al., 1998). However, few epidemiological studies have explored the association between exposure to neuroleptics and mortality. Wad-

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dington et al. (1998) have found in elderly subjects with schizophrenia a 2.5-fold increased risk of death for each added neuroleptic. No previous epidemiological study has assessed whether the excess mortality due to neuroleptics may be or not restricted to some class of neuroleptics.

We therefore looked for an association between the number and nature of neuroleptics and mortality in a cohort of patients with schizophrenia.

2. Methods

This work was done in a fixed cohort of patients with schizophrenia, which started in 1993. This cohort was implemented and is followed by F. Casadebaig and A. Philippe to assess causes of death and access to medical care of patients with schizophrenia.

2.1. Population and data sources

Source population of the cohort is all patients with schizophrenia followed, as out or in-patients, in French public departments of adult general psychiatry, each of which has a geographically defined catchment area of about 70 000 inhabitants ("public psychiatry sectors" or "sectors").

Volunteer participation to this cohort was proposed to the heads of departments in psychiatric journals. Overall, 122 of 800 "sectors" (15.3%) agreed to participate and recruit patients.

The inclusion time of patients was spread over 1 to 3 months. Psychiatrists from the sectors included all patients fulfilling the following criteria: (i) having a diagnosis of schizophrenia according to ICD-10 F20 (International Classification Diseases, 10th edition; WHO); (ii) being followed in general psychiatric "sector" as outpatient, or as part-time or full-time in-patient for less than 1 year; (iii) having given agreement to participate in the study; and (iv) having a civil registration available in France (Casadebaig and Philippe, 1999).

Patients totaling 3474 to were recruited by 122 psychiatric sectors, constituting the initial cohort.

One hundred and forty-nine patients (4.3%) followed by psychiatric sectors which withdrew participation after 2 years or less were excluded from the present study.

2.2. Data

Baseline data were collected at the onset of the cohort in 1993 using a standardized questionnaire. The data recorded were:

- demographic: age, sex, educational level;
- behavioral risk factors: previous history of suicide attempt, illicit drug abuses (as indicated by the subjects), alcohol (using the CAGE questionnaire (Ewing, 1984)) and tobacco consumption;
- degree of mental suffering as assessed by the psychiatrist according to a four-level range: absent, moderate, great and extreme;
- data on physical health status: height, weight (body mass index, BMI), previous medical history and concomitant diseases;
- date of the first psychiatric hospitalization; and
- psychotropic medication at inclusion (name and dosage of drugs).

Data concerning drug prescription and other variables (data on somatic diseases, risk behaviors and psychotropic treatments) were updated in 1996. Update data were missing in 913 patients lost to follow-up by the sectors.

2.3. Causes of death

All sectors were contacted on a yearly basis to ascertain life status of the patients. For patients lost to follow-up or for whom positive life status information was lacking, the town clerk of the town of birth was contacted to ascertain life status.

For all patients identified as having died, date and cause of death were retrieved from the psychiatric sector team and from the official death certificate (Casadebaig and Philippe, 1999).

Causes of death were coded and inputted into the database using the ICD9 classification (International Classification Diseases, ninth edition; WHO).

For the purpose of the present study, we have reclassified deaths into three main categories:

- suicide if cause of death was coded E950–E959 in the death certificate or if the sector mentioned a suicide while the official cause was undetermined or an accident;

Table 1
Demographic characteristics and health status of patients

Mean age (SD)*	At inclusion ($n=3325$)		At update ($n=2412$)	
	39.3 (11.4)		42.8 (11.3)	
	n	%	n	%
Male gender	2127	64.0	1546	64.1
Body mass index (BMI) > 30	415	12.5	330	13.7
Previous suicide attempt	1072	32.3	800	33.2
Treatment setting				
Hospital	1237	37.2	880	36.5
Ambulatory	2087	62.8	1531	63.5
Duration of disease (years)*				
0 to 5	912	28.3	269	11.5
6 to 10	718	22.3	550	23.4
>10	1587	49.3	1528	65.1
Diabetes	72	2.2	73	3.0[†]
Other diseases	613	18.4	396	16.4[†]
Concomitant physical illness(es)	874	26.3	613	25.4
Degree of psychic suffering				
Absent	819	24.6	612	25.4
Moderate	1772	53.3	1292	53.6
High	725	21.8	466	19.3

* Significance not tested.
[†] $p<0.05$, update vs. inclusion.

- determined (coded 410–438) and undetermined (coded 785, 798, 799) cardiovascular death;
- other causes.

2.4. Ethics and confidentiality

All patients gave informed oral consent to participate in the study. Data confidentiality processes were approved by the National Committee on Informatics and Liberties (CNIL).

3. Statistical analysis

3.1. Variables

The dependent variable was life status (including subanalyses of causes of death) Main explicative variable was neuroleptic class categorized as "phenothiazines", "butyrophenones", "benzamides", "thioxanthenes" or "other neuroleptics" (i.e. olanzapine, clozapine, risperidone, loxapine, pimozide). For each

Table 2
Mortality by cause

Causes of death	1993–1996 ($n=3325$; 147 deaths)			1993–1996[a] (yearly)		1996–1997 ($n=2412$; 31 deaths)		
	n	%[b]	%[c]	n	%[b]	n	%[b]	%[c]
All causes	147	4.4	100	49	1.5	31	1.3	100
Suicide	70	2.1	47.6	23.3	0.7	12	0.5	38.7
CV undetermined	8	0.2	5.4	2.7	0.08	4	0.2	12.9
CV determined	8	0.2	5.4	2.7	0.08	2	0.1	6.5
Others causes	61	1.8	41.5	20.3	0.6	13	0.5	41.9

CV: cardiovascular.
[a] Numbers found by dividing the total number of deaths by 3.
[b] Percentage of the total population.
[c] Percentage of the total number of deaths.

class, patients were classified into users and non-users. User or non-user status for a given class was independent from the fact that other neuroleptic(s) may be used concomitantly by the patient. Therefore, we also defined a binary variable coding for multiple neuroleptic use (number of neuroleptics ≤ 1; number of neuroleptics >1 (2 to 5)).

Potential confounding factors that were tested were age, gender, educational level (no schooling, primary or specialized schooling, apprenticeship and technical training, secondary school and above), duration of disease (less than 5 years, 6 to 10 years and more than 10 years) and degree of mental suffering (absent, moderate, high (pooling great and extreme)).

Treatment setting (ambulatory or hospitalization), BMI (obese: BMI ≥ 30 (James, 1996; Lissner et al., 2000)), number of neuroleptics used ($n \leq 1$; $n > 1$) were coded as dichotomous variables, same with behavioral risk factors such as drugs, alcohol and tobacco use, previous suicide attempt, used of antidepressants and other psychotropic drugs, and comorbidities (vascular and respiratory diseases, cancer, diabetes, epilepsy, AIDS and others).

A binary variable identified initial data from update data.

3.2. Analysis

EPI-INFO version 6.04c fr (Centers For Disease Control & Prevention (CDC), USA) and EGRET software (Epidemiological Graphics, Estimation, and Testing package—versions 0.19.6 and 0.26.6, SERC) were used. For statistical analysis, the significance of the p-value was established at the 5% level.

The chi-square test for qualitative variables and ANOVA for quantitative variables studied the distribution of main subject characteristics for each class of neuroleptic. The exposed groups were made of patients having used at least one neuroleptic of the considered class alone or in association with other neuroleptics. The control group was subjects not treated by this class of neuroleptics.

The analysis of the relationship between global mortality and neuroleptic class was done by adjusting five (one for each class of neuroleptic) unconditional logistic regression models according to Hosmer and Lemeshaw's (1989) step-by-step down process.

The results were adjusted for the potential confounding factors (risks factors for deaths) available in the cohort data. Some of these were maintained in the models during all steps of iterations even if they were not significant (forced variables). We also introduced a variable distinguishing the two study periods (follow-up from 1993 to 1996 and from the update in 1996 to 1997) to neutralize a possible survival bias, since patients who had updated data were survivors of the cohort followed during the first period.

This analysis was done for all-cause mortality and for mortality by suicide, determined and undetermined cardiovascular causes and other causes.

4. Results

Among 3474 patients included in the cohort, 3325 (95.7%) were eligible for our study (follow-up >2 years). Of these, 2412 (72.5%) were updated in 1996. Compared to eligible subjects at inclusion, the 149 patients excluded from this study were more often antidepressant users and less often phenothiazines users. A higher proportion had previously attempted suicide, were never schooled or had secondary or above educational level. The excluded subjects were not different in terms of the other characteristics.

Table 3
Use of neuroleptics and other psychotropic drugs

	At inclusion ($n=3325$)		At update ($n=2412$)	
	n	%	n	%
Neuroleptics	3203	96.3	2300	95.4
Number of Neuroleptics >1 (2 to 5)	1714	51.5	1082	44.9*
Phenothiazines	2062	62.0	1371	56.8*
Butyrophenones	1359	40.9	891	36.9*
Benzamides	425	12.8	288	11.9
Thioxanthenes	311	9.4	259	10.7
Other neuroleptics	430	12.9	309	12.8
Antidepressants	670	20.2	456	18.9
Other psychotropic drugs	2474	74.4	1838	76.2

* $p<0.001$, update vs. inclusion.

4.1. Study population

The characteristics of patients at inclusion and at update are presented in Table 1. There was no difference between the initial data and updated data, except for the time-dependent variables (age, duration of disease), and for the neuroleptic use profile (see below).

4.2. Death and causes of death

Between inclusion and 1997, 178 patients died, representing 4.4% of subjects over 1993–1996 and 1.3% of the patients in 1996–1997 (Table 2).

Overall death rate did not change over time.

Suicide was the first cause of death during the first 3 years of follow-up, slightly decreasing thereafter,

Table 4
Subject characteristics according to neuroleptic class (mean percentage of pooled initial (3325) and updated (2415) patients)

	Phenothiazine		Butyrophenone		Benzamide		Thioxanthene		Other	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Users number	3433	2304	2250	3487	713	5024	570	5167	739	4998
Mean age (SD or range[a])	41.8** (11.6)	39.2 (11.2)	40.9 [17–85]	40.6 [17–86]	38.6** (11.0)	41.0 (11.5)	39.1** (11.1)	40.9 (11.5)	39.1** (11.2)	41.0 (11.5)
	%		%		%		%		%	
Male gender	66.0**	61.1	63.6	64.3	68.2*	63.4	60.9	64.4	63.5	64.1
BMI>30	13.8*	11.8	13.7	12.5	10.1*	13.4	9.6*	13.4	15.7*	12.6
Educational level										
None	1.6	1.3	1.7	1.4	1.4	1.5	1.2	1.5	1.1	1.5
Primary	41.9	32.9	38.8	37.9	32.1	39.1	35.8	38.5	37.0	38.4
Apprenticeship	21.8	22.8	21.7	22.6	21.5	22.3	22.6	22.2	24.8	21.8
Secondary and above	34.6*	43.1	37.8	38.2	45.0	37.0	40.4	37.8	37.1	38.2
In-patient treatment	38.4*	34.5	38.2	36.1	41.2*	36.3	43.7**	36.2	44.6**	35.8
Duration of the disease (years)										
0 to 5	17.8	26.4	22.7	20.3	28.9	20.2	23.4	21.0	19.2	21.5
6 to 10	20.8*	25.8	22.9	22.7	26.1	22.3	21.8	22.9	25.7	22.4
>10	61.4**	47.8	54.4	57.0	45.0**	57.5	54.7	56.1	55.1	56.1
Mental suffering										
Absent	24.4	26.3	24.7	25.4	23.0	25.5	24.8	25.2	24.2	25.3
Moderate	54.5	53.0	53.8	53.9	53.0	54.0	55.2	53.7	48.9	54.6
High	21.1	20.7	21.5	20.6	24.0	20.5	20.0	21.1	27.0*	20.0
Alcohol use	16.6*	14.5	17.3*	14.7	11.3**	16.4	15.7	15.7	14.8	15.9
Tobacco use	57.1	56.2	57.9	55.9	53.9	57.1	62.9*	56.0	58.2	56.5
Drug abuse	5.2**	7.5	6.9*	5.6	6.3	6.1	7.8	5.9	4.8	6.3
Suicide attempts	34.1*	30.6	31.4	33.5	34.1	32.4	31.1	32.9	38.7**	31.8
Cancer	0.4	0.8	0.8*	0.4	0.3	0.6	0.7	0.5	0.8	0.5
Diabetes	2.5	3	2.8	2.3	2.1	2.6	2.6	2.5	2.0	2.6
Epilepsy	1.3	1.1	1.2	1.2	1.4	1.2	1.6	1.2	1.1	1.2
Respiratory diseases	3.1	2.9	3.0	3.0	3.1	3.0	2.6	3.0	2.4	3.1
Vascular diseases	5.4	5.3	6.3*	4.7	5.0	5.4	4.6	5.4	4.6	5.4
AIDS	0.3*	0.7	0.6	0.3	0	0.5	1.2*	0.3	0.3	0.5
Other diseases	17.7	17.5	17.5	17.7	18.7	17.4	17.5	17.6	16.4	17.8
Comorbidities ≥ 1	25.8	26.1	26.8	25.3	25.7	25.9	25.8	25.9	25.3	26.0
Antidepressant use	21.2**	17.3	16.7**	21.5	20.2	19.5	19.1	19.6	18.7	19.8
Other psychotropic drugs use	81.2**	66.2	77.5**	73.7	73.6	75.4	76.1	75.0	71.3*	75.7
No. of neuroleptics >1	73.8**	11.4	62.6**	39.8	54.8**	47.9	46.0	49.0	54.7**	47.9

[a] The range is given when the age distribution is not Gaussian.

* $p < 0.05$.

** $p < 0.001$, users vs. non-users of each neuroleptic class.

representing 54.3% of all deaths in the first year of follow-up, 45.1%, 45.8% and 31.7%, respectively, during the second and the third year of follow-up and after update.

Cardiovascular death represented a small proportion (11%) of all deaths during the first 3 years of follow-up, increasing after follow-up to 17.4% of all deaths, and especially for undetermined cardiac deaths (Table 2).

The risk of dying increased with illicit drug abuse (OR=2.25; 95% CI 1.34–2.57), previous suicide attempts (OR=1.89; 95% CI 1.34–2.57), male gender (OR=1.72; 95% CI 1.23–2.44) and age (OR/year=1.03; 95% CI 1.01–1.04).

4.2.1. Use of neuroleptics and other psychotropic drugs

At baseline, 96.3% of patients were using neuroleptics, mostly phenothiazines (62%) and butyrophenones (41%). Slightly more than half were using two or more neuroleptics simultaneously, 20% were using antidepressants concomitantly and 74% other psychotropic agents (Table 3).

At follow-up, information on the neuroleptics used was missing for eight patients. The overall prevalence of neuroleptic use was similar to that of baseline (95.4% of all patients), but with fewer multiple neuroleptic users and fewer users of phenothiazines (57%) and butyrophenones (37%), the use of the other drugs being essentially unchanged. A total of 1750 patients (53%) switched drug classes between inclusion and update.

4.3. Profile of neuroleptics users according to class

4.3.1. Phenothiazines

Compared to non-users, phenothiazine users were older, more often obese, had a lower educational level, were more often followed as outpatients and had a longer duration of disease. There were more alcohol drinkers and less illicit drug users. More had previous suicide attempt and fewer had acquired immune deficiency syndrome (AIDS). They were the ones who most often used concomitant psychotropic drugs.

Almost three-quarters of these patients also used other neuroleptics (Table 4).

4.3.2. Butyrophenones

Butyrophenone users were more often alcohol drinkers and less often drug abusers, and others were psychotropic drug users. Associated vascular diseases and cancer were more frequent.

4.3.3. Benzamides

Benzamide users were younger, more frequently male, less frequently obese and more frequently followed as outpatients. They had been more recently diagnosed and were more frequently on polytherapy.

4.3.4. Thioxanthenes

Compared to non-users, thioxanthene users were younger, less frequently obese, more frequently smokers, AIDS and hospitalized subjects.

Table 5
Causes of deaths according to neuroleptic class (percentage of pooled initial (3325) and updated (2412) patients)

	Phen (%)		Buty (%)		Benz (%)		Thiox (%)		Others (%)	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Users number	3433	2304	2250	3487	713	5024	570	5167	739	4998
Causes of death										
Overall deaths	3.26	2.86	2.79	3.33	2.38	3.20	4.21	2.98	3.52	3.04
Suicide	1.51	1.30	1.2	1.58	1.26	1.45	2.63	1.30	1.08	1.48
CV determined	0.18	0.17	0.13	0.20	0.28	0.16	0	0.19	0.13	0.18
CV undetermined	0.26	0.13	0.31	0.14	0	0.24	0.35	0.19	0.27	0.20
Others causes	1.28	1.30	1.11	1.41	0.84	1.35	1.23	1.30	2.03	1.18

Phen: phenothiazines; buty: butyrophenones; benz: benzamides; thiox: thioxanthenes.
CV: cardiovascular.

Table 6
Multivariate analysis of mortality risks according to neuroleptic class

	Number of deaths	Crude odds ratio		Adjusted odds ratio		
		OR	[95 % CI]	OR	[95% CI]	*p*
All causes						
Phenothiazines (1)	112	1.08	[0.79–1.48]	1.00	[0.67–1.47]	0.99
Butyrophenones (2)	62	0.79	[0.58–1.08]	0.77	[0.55–1.1]	0.12
Thioxanthenes (3)	24	1.50	[0.96–2.33]	1.59	[1.02–2.50]	0.04
Benzamides (4)	17	0.72	[0.43–1.20]	0.76	[0.45–1.23]	0.29
Others (5)	26	1.16	[0.75–1.78]	1.25	[0.81–1.9]	0.31
Suicide						
Phenothiazines (1)	52	1.09	[0.70–173]	1.17	[0.66–2.08]	0.59
Butyrophenones (2)	27	0.72	[0.45–1.14]	0.69	[0.43–1.13]	0.15
Thioxanthenes (3)	15	2.17	[1.23–3.83]	2.22	[1.24–3.97]	0.007
Benzamides (4)	9	0.84	[0.42–1.70]	0.81	[0.40–1.64]	0.56
Others (5)	8	0.72	[0.35–1.51]	0.68	[0.32–1.43]	0.31
Other causes[a]						
Phenothiazines (1)	44	0.93	[0.58–1.49]	0.71	[0.39–1.28]	0.26
Butyrophenones (2)	25	0.76	[0.47–1.23]	0.77	[0.46–1.28]	0.31
Thioxanthenes (3)	7	0.98	[0.45–2.16]	1.03	[0.46–2.30]	0.95
Benzamides (4)	6	0.61	[0.26–1.40]	0.77	[0.33–1.80]	0.55
Others (5)	15	1.73	[0.98–3.08]	2.06	[1.15–3.70]	0.02

[a] Death from causes other suicide or cardiovascular causes.
Adjustment variables other than those which were forced (age, gender, previous suicide attempts, number of neuroleptics, concomitant disease, duration of disease):

Model	All causes of death	Suicide	Other causes
(1)	Cancer, drug abuse, AIDS	Drug abuse	Antidepressants, AIDS, cancer
(2)	Cancer, drug abuse	Drug abuse	Cancer, antidepressants, AIDS
(3)	Drug abuse	Tobacco, drug abuse	AIDS
(4)	Treatment setting		AIDS
(5)	Drug abuse		

4.3.5. Other neuroleptics

Patients treated by "others classes of neuroleptics", compared to non-users (typical neuroleptic users), were younger, more frequently obese and hospitalized. More patients using newer neuroleptics had a high degree of mental suffering. They also had more frequently suicide attempts and neuroleptic polytherapy. Fewer took other psychotropic drugs.

4.4. Neuroleptic classes and mortality

The distribution of causes of deaths in users and non-users of the various neuroleptic classes is shown in Table 5. The results of multivariate logistic regression analysis are shown in Table 6.

Thioxanthenes were the only neuroleptics that were associated with increased overall mortality in the multivariate analysis (OR = 1.59; 95% CI 1.02–2.50; $p = 0.04$). This was related to a significant association with suicide (OR = 2.22; 95% CI 1.24–3.97; $p = 0.006$) but not with other causes of death. Users of "other neuroleptics" had an increased risk of dying from causes other than suicide or cardiovascular causes (OR = 2.06; 95% CI 1.15–3.70; $p = 0.016$).

None of the neuroleptic classes was associated with an increased risk of cardiovascular death (determined or undetermined).

There was no association of increased risk of death with the use of two or more neuroleptics.

5. Discussion

Our study found an increased risk of global mortality, related to an increased risk of suicide users of thioxanthenes, after adjustment for a number of possible confounding variables.

Deaths from causes other than suicide or cardiovascular causes occurred more frequently in patients treated by atypical neuroleptics.

There were no differences between neuroleptic classes for cardiovascular deaths.

We did not confirm the association between exposure to multiple neuroleptics and excess mortality found by Waddington et al. (1998).

To explore the influence of neuroleptics on mortality in schizophrenic patients, the best method would be to compare the use with the non-use of neuroleptics. However, in current clinical practice, it is very difficult to find a group of untreated schizophrenic patients large enough to perform proper analysis. At inclusion, only 3.7% of our patients had no neuroleptics. Therefore, we really had no choice but to compare user with non-users for each class of neuroleptics, non-users being in fact users of other classes of neuroleptics.

We have little reason to suspect that ascertainment or classification biases may have influenced the present findings: data on drug use were collected prospectively before knowing the life status of the subjects or the cause of death. Moreover, because the cohort was originally constituted to study access to care of patients with schizophrenia, using causes of death as an indicator of effectiveness of care policy, investigators were blind to the hypothesis tested in the present study. Data collection was not influenced by a possible link between treatment by neuroleptics and the occurrence of deaths. Classification of cause of death was done without knowledge of exposure status.

For patients lost to follow-up or for whom positive life status information was lacking, the town clerk of the town of birth was contacted to ascertain life status. Therefore, no death would easily escape the investigators' notice.

However, because of the timing of data ascertainment, drug treatments taken into account in the analyses describe the situation at the set points (at inclusion and at update) but were not necessarily the data that would have been collected at the index date, i.e. at the time of death.

Moreover, we did not consider the kind of neuroleptic class associations, dosages or the use of anticholinergic drugs. For suicide death in a case-control study, Taiminen and Kujari (1994) found more often lower neuroleptic doses in the suicide than in the control group, even if they suggested that it was more probably linked with the differences in the symptom profiles.

It was also impossible to take into account the nonpsychotropic treatments for other diseases because these data were not collected in the questionnaire of the updated set. The existence of concomitant diseases was used as a proxy measure of this potential confounding factor. No association was found between mortality and concomitant diseases.

5.1. Effects of thioxanthenes on suicide

The increased overall mortality in thioxanthene users was entirely explained by the increased suicide mortality. Beyond a possibly real effect of thioxanthenes on the risk of suicide, these results could be explained by a prescription bias if thioxanthenes were preferentially used in subjects at higher risk of suicide, e.g. because of added depression.

Some studies have suggested that thioxanthenes may reduce the intensity of depressive symptoms or the risk of suicide. A multi-center study on acute psychotic states found that zuclopenthixol caused a significantly greater improvement in the 'anxious-depression' factor than haloperidol (Heikkila et al., 1992). Montgomery (1997) reported that a low dose of flupenthixol in depressed patients with a history of suicide attempts decreased the suicide attempt rate compared to placebo.

Though thioxanthenes are licensed in some countries for depression, this is not the case in France. However, French psychiatrists could have been informed of the potential effect of thioxanthenes on depressive symptoms and this could result in preferential use in patients with schizophrenia and concomitant depression. Though there was a non-significantly higher number of patients with moderate level of mental suffering in thioxanthene users, the lower rate of previous suicide attempts and the lesser concomitant use of antidepressant drugs in thioxanthene-treated patients do not support the hypothesis of a prescription bias. However, we cannot definitely

exclude that clinicians may be less likely to prescribe antidepressants in patients treated with thioxanthenes because of the purported antidepressant effect of flupenthixol and zuclopenthixol. Thus, these patients may be at increased risk of suicide because they do not receive an adequate treatment when depressed, since the antidepressant effect of thioxanthenes is far from being confirmed in large samples of subjects with schizophrenia and depression.

Only a study focusing on prescription or on intent to prescribe would allow to identify a bias linked with the perception of a different effectiveness.

5.2. Other results

No definite interpretation can be proposed with regard to the fact that mortality from "others causes" occurred more frequently in "other neuroleptic" users. This group includes products with different pharmacological effects (olanzapine, clozapine, risperidone, loxapine, pimozide). Nevertheless, we can note a higher number of obese patients, a well-known side effect of some antipsychotic drugs particularly novel ones (Ganguli, 1999; Kawachi, 1999), which could increase the risk of "natural" causes of deaths.

Another phenomenon could mask the possible link between the other classes of neuroleptics and the occurrence of death. Neuroleptics mostly inhibit dopamine transmission but also act on other neurotransmitter receptors and mechanisms, resulting in different pharmacological or side effect profiles. The classification used for this study, the Vidal Dictionary (Anon., 2000) and ATC classification (Anatomical Therapeutical and Chemical classification 2000), includes in some classes chemically similar but pharmacologically disparate products. These pharmacological differences could result in risk differences, making a whole class not at risk because individual products in this class could have opposed effects. It is noteworthy that the main significant class only counts two distinct but closely related and very similar molecules (fluopenthixol, zuclopenthixol), which is not the case for phenothiazines (nine products), butyrophenones (four products), benzamides (four products), and other neuroleptics (five products). A more discriminating study on individual products would allow to define these risks better and those of their associations. However, our cohort was not powered to evaluate individual drug risks, or the effect of drug associations.

5.3. Relevance of these results to the general populations of schizophrenic patients

To ensure the generalisability of our findings, we compared subjects' characteristics with results of previous studies. The patients included in the cohort were followed by publics sectors of psychiatry. In public sectors, the treatment setting may preferentially include subjects presenting with more severe forms of schizophrenia, and from the more disadvantaged social categories than subjects treated in private practice.

Despite this, the present cohort seems reasonably representative of patients with schizophrenia:

- mainly male gender (Jablensky, 1995)
- with classics risk factors for death in this population: age, gender, suicide attempt, drug abuse (Ginestet, 1997; Rossau and Mortensen, 1997)

and a pattern of neuroleptic use close to that found by Fourrier et al. (2000) in 1996, with 53% monotherapy, 60.8% phenothiazines, 35.2% butyrophenones and 9.6% thioxanthenes, but with more benzamides and "other neuroleptics" (respectively 20% and 27% of patients) than in the present study. This difference may be related to the treatment setting, which in that study was predominantly in full-time or part-time private practice.

5.4. Conclusion

Our data confirm that death rates are high in patients with schizophrenia and that the main cause of death is suicide, representing almost half of all deaths.

Thioxanthenes were associated with an increased risk of suicide which in turn increased all-cause death. The use of neuroleptics with a purported antidepressant effect does not avoid this cause of death and could even increase it. It is however not possible to exclude a prescription bias. In the same way, the increased risk of other cause death with other neuroleptics including atypicals is unexplained. It is necessary to continue careful evaluation of other cause

mortality with atypical drugs, particularly pulmonary thromboembolism (Coodin and Ballegeer, 2000; Hagg et al., 2000) and cancer.

Until the appropriate comparative clinical trials are performed, further studies of existing databases could give some help or indications as to, for example, selective prescribing, or the effect of neuroleptic associations.

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