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ORIGINAL PAPER

The European Post-marketing Observational Sertindole Study: an investigation of the safety of antipsychotic drug treatment

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Abstract The objective of the European Post-marketing Observational Serdolect® (EPOS) Study was to compare the safety of treatment with Serdolect (sertindole) with that of usual treatment in patients with schizophrenia, in normal European clinical practice. The EPOS was a multicentre, multinational, referenced, cohort study. Patients were enrolled at 226 centres in ten European countries. The study was prematurely terminated in 1998 as a result of the temporary market suspension of sertindole. Termination of the study reduced the number of patients recruited from the planned 12,000 to 2,321. While the power of the study was weakened, it did provide useful mortality information, which may be useful for future long-term studies. Crude mortality in the sertindole and non-sertindole groups was 1.45 (95% confidence interval, CI 0.53–3.16) and 1.50 (CI 0.72–2.76) deaths/100 patient-years exposed, respectively. There were no more cardiac deaths in the sertindole group than in the non-sertindole group. QT interval prolongation did not translate into an increased risk of death. Sertindole was well tolerated and caused few extrapyramidal symptoms. Although CIs remained large, this post-marketing study does not provide any evidence against the use of sertindole under normal conditions. Sertindole was well tolerated and posed no significant safety problems.

Keywords Sertindole · EPOS · Antipsychotic · Safety · Mortality

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Introduction

Sertindole (Serdolect®, H. Lundbeck A/S, Copenhagen, Denmark) is a limbic-selective antipsychcotic drug with a high affinity for serotonin 5-HT_2, adrenergic α_1 neuroreceptors, and for dopamine D_2 receptors [1, 2]. It has a weaker affinity for dopamine D_1 receptors and has no, or low, affinity for 5-HT_{1A} receptors, α_2-adrenoreceptors, β-adrenoreceptors, histamine H_1, sigma, and muscarinic cholinergic receptors [2]. The drug displays high levels of clinical efficacy against the positive symptoms of schizophrenia, efficacy against the negative symptoms, and good tolerability with few extrapyramidal symptoms (EPS), no anticholinergic side effects, and some weight gain [3–8].

The European Post-marketing Observational Serdolect (EPOS) study was part of a group of four post-marketing studies designed to provide further information on the drug's profile [9–11]. This particular study was concerned specifically with safety under normal clinical practice conditions and also aimed to provide extensive epidemiological information on the treatment of patients with schizophrenia in Europe. It was designed to include a total of 12,000 patients recruited in 13 European countries, and to follow patients for at least 1 year of therapy. The study comprised two groups of patients with schizophrenia—those receiving sertindole (the sertindole group) and those receiving antipsychotic treatments other than sertindole or no treatment for schizophrenia (the reference non-sertindole

group). There were twice as many patients recruited to the reference group as the sertindole group. The reference group population would have been sufficiently large to enable adequately powered statistical analyses of several different patient sub-groups, in comparison with similar groups in the sertindole population.

Had the study been completed, it would have been the first prospective, long-term, observational study in schizophrenia with a reference group. As a result of the temporary suspension of sertindole from the market, the study was prematurely terminated on 1 December 1998, less than 18 months after it had begun recruitment. The study was terminated before the planned sample size was achieved to enable appropriate power for the statistical analysis. Nonetheless, the study provides reliable mortality data and, given that sertindole was reintroduced into the European market in 2005, that information could be relevant for the medical and scientific community.

Methods

Study design

The EPOS study was a multicentre, multinational, post-marketing, referenced, cohort study on the safety of the antipsychotic drug sertindole in the treatment of schizophrenia. The first phase of recruitment took place in the UK, Austria, Denmark, Finland, Germany, The Netherlands, and Ireland. Second-phase countries were Greece, Italy, and Spain, followed by a third phase in Norway, Belgium, and Switzerland. Ultimately, Norway, Belgium, and Italy did not recruit patients into the study before it was discontinued. Recruitment to the study began in the UK in July 1997.

All patients with schizophrenia, and not currently treated with sertindole, were eligible to take part, but all patients, or their legal representative, were required to give their informed consent. The study comprised two groups—the sertindole group and the reference non-sertindole group. Patients in the sertindole group received sertindole treatment according to the Summary of Product Characteristics (SPC) [12], while those in the non-sertindole group received usual care—a schizophrenia treatment other than sertindole, or treatments not including medication. Patients were recruited to either the sertindole group or the non-sertindole group in the ratio 1:2 (sertindole:non-sertindole). The reason for including a large cohort and twice as many non-sertindole patients was to ensure sufficient patients to enable comparisons between the sertindole group and sub-groups of matched patients selected from the non-sertindole group.

Each investigator recruited a maximum of 15 sertindole patients and 30 non-sertindole patients. Since the aim was to build an unbiased reference cohort, patients in the non-sertindole group were randomly selected at each study site without the use of any selection criteria. Patients recruited to the sertindole group were those whom investigators would have prescribed sertindole as part of their normal clinical practice, but excluded those already taking sertindole. The sertindole group was therefore not randomly selected.

The non-sertindole cohort was a representative sample of patients treated according to usual care. Irrespective of any treatment changes they were followed for the entire duration of the study unless they withdrew consent. Therefore, even if they discontinued their treatment and switched to a new medication they were still considered part of the study. In contrast, in the sertindole cohort, if patients discontinued sertindole they were withdrawn from the study and considered as premature study discontinuations. In this case, they were followed for up to 30 days after withdrawal; any event happening during these 30 days was attributed to sertindole.

One of the aims of the study was to build a picture of real-life clinical practice in the treatment of schizophrenia and, therefore, investigators were required to record data as part of their normal clinical practice—visits were not predefined in the protocol. Patients also obtained their drugs in the usual manner, e.g. from the hospital or from a pharmacy.

Study consistency

A project group set up by H. Lundbeck A/S oversaw the study and ensured that the study protocol and study procedures were consistently interpreted across Europe. The group undertook patient monitoring, data management, statistical analysis, and quality control. Adverse events (AEs) were categorized according to the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), the Food and Drug Administration's system for coding of post-marketing adverse reaction reports. An independent advisory safety committee was also set up to review all data from a safety and ethical perspective. The committee was comprised of five experts in psychiatry, cardiology, clinical pharmacology, pharmacoepidemiology, and biostatistics.

Written approval was received for this study from the Independent Ethics Committee (IEC) or the Institutional Review Board, except for in Austria and Germany, which did not require IEC approval. The project was nevertheless submitted for notification in these countries.

Data and statistical analysis

Baseline data collected included: demographic information, social and medical history, current status and the essential features of the psychiatric diagnosis, severity of

illness, treatment (drugs, dosages), and additional therapy (such as occupational therapy and psychotherapy). The diagnosis of schizophrenia was not defined by DSM-IV or ICD-10 criteria, as not all psychiatrists are familiar with these classification systems. Patients were diagnosed according to the psychiatrist's experience and clinical judgement, or by using a classification system to which they were accustomed. Measuring of vital signs was recommended and results of clinical laboratory investigations (e.g. haematology, biochemistry) were recorded whenever they were performed during the study. Patients also underwent a physical examination and an electrocardiogram (ECG). A second ECG was carried out after approximately 3 months. All sertindole patients also had an ECG recording at discontinuation from the study. Throughout the study, patients were assessed according to the investigator's usual clinical practice. In addition to the ECG recordings, other data recorded during the study included: AEs (symptoms, time of onset, duration, severity, relationship to drug, action taken), duration of hospitalization, concomitant medication, and other therapies. As at enrolment, measuring of vital signs was recommended and results of any clinical laboratory investigations were recorded. Since the two study groups were selected differently, it was intended that they would be analysed separately using descriptive statistics. Data from comparable sub-groups would have also been analysed in this way. Stratification and the inclusion of relevant covariates in the statistical model would have enabled the risk factors in each group to be adjusted and for the two study groups to be compared in a meaningful way.

The known QTc prolongation effect of sertindole is directly related to the plasma concentration of the drug; when treatment is withdrawn, the plasma concentration reduces according to the half-life of 2–3 days. By the end of a 5-day sertindole-free period, the potential QTc prolongation effect would be significantly lowered. A period of 5 days after drug discontinuation was therefore chosen a priori to be used in the analysis of crude mortality rates.

QTc interval categories were defined according to CPMP Guidelines, 'prolonged' being >470 ms in females and >450 ms in males.

Results

Changes to the planned analysis

Since the EPOS study was prematurely terminated, the number of patients recruited was considerably less than intended and most did not complete the full observation period. As a result, the power of the study was weakened and the two study groups were not large enough to allow subgroup analysis. Therefore, no formal statistical analyses or comparisons between treatment groups were performed and data are simply tabulated and described. For economy of space, data from both groups are presented side by side in the following tables, but no inference of comparison should be taken due to the partially non-randomized nature of the study. The reference group was not intended to be directly compared with the sertindole group, and is therefore referred to as the 'non-sertindole' group.

Deviations to the protocol that prevented strict definition of the treatment groups, baseline, and study period were as follows: sertindole patients who stopped treatment or took drug holidays were not excluded from the sertindole group; non-sertindole patients were allowed to start sertindole during the study period [there were 24 such patients and they were retained in the reports of the non-sertindole group, however none of these patients died or had sertindole-related serious AEs (SAEs)]; some sertindole patients began treatment before or after the enrolment visit; not all patients attended a final study-discontinuation visit so the last visit was not always the same as the discontinuation date.

Patients

A total of 2,321 patients were enrolled (1,064 sertindole patients and 1,257 non-sertindole patients) at 226 centres in ten European countries. As the study was prematurely terminated, the proposed patient sertindole:non-sertindole ratio of 1:2 was not achieved, and only 140 patients completed the full observation period (Table 1). The two groups differed in that, on average, patients in the sertindole group were younger than those in the non-sertindole group and the female:male ratio was higher in the sertindole group. Patients in the sertindole group were more likely to be hospitalized at enrolment, and to be experiencing their first episode of the illness. In comparison, more patients in the non-sertindole group had been ill with schizophrenia for more than 10 years (Table 2).

Concurrent illnesses

Concurrent illnesses in both groups are displayed in Table 3.

Concomitant medication

The number of concomitant medications taken by patients in each study group differed considerably and patients in the sertindole group took a greater number of concomitant drugs. In the sertindole group, 49% of the patients started treatment with four or more drugs, and 15% of the patients took four or more concomitant antipsychotics during the

Table 1 Number of patients who completed and did not complete the EPOS study in each study group

	Sertindole group *n* (%)	Non-sertindole group *n* (%)
Patients enrolled	1,064	1,257
Patients who took sertindole	1,053	24[b]
Completed observation period	64 (6)	76 (6)
Non-completers		
Due to termination of the study	915 (86)	1,128 (90)
Those enrolled for >1 year	112	110
Premature discontinuations	85 (8)	53 (4)
Due to death	10	9
Due to being lost to follow-up	16	19
Due to patient withdrawing consent	59[a]	25[c]

[a] One patient died 2 months after withdrawing consent

[b] These patients are deviations from the protocol; however none of these 24 patients died or had sertindole-related SAEs

[c] One patient died 3 months after completing the study

observation period. In contrast, only 19% of the patients in the non-sertindole group started treatment with four or more drugs, and 4% took four or more concomitant antipsychotics during the observation period. Nine patients in the non-sertindole group (1%) did not take any medication.

Duration and type of antipsychotic treatment

In the sertindole group, the mean treatment duration was 144 days (1–563 days), which represents 414 patient-years exposed (PYE). The most commonly prescribed antipsychotics in addition to sertindole were olanzapine ($n = 311$, 62 PYE), risperidone ($n = 257$, 45 PYE), haloperidol/haloperidol decanoate ($n = 179$, 34 PYE/$n = 31$, 9 PYE), clozapine ($n = 120$, 35 PYE), and levomepromazine ($n = 123$, 35 PYE). In the non-sertindole group, the most commonly prescribed antipsychotics were clozapine ($n = 295$, 134 PYE), olanzapine ($n = 309$, 110 PYE), risperidone ($n = 243$, 90 PYE), haloperidol/haloperidol decanoate ($n = 183$, 54 PYE/$n = 90$, 27 PYE), and levomepromazine ($n = 138$, 52 PYE).

Protocol deviations

Apart from the change in population size, other protocol deviations were as follows: for 50 patients in the sertindole group and 52 in the non-sertindole group, the primary psychiatric diagnosis was not schizophrenia. Since it was unlikely to affect the results, the patients for whom the primary psychiatric diagnosis was not schizophrenia were included in their respective study groups.

Table 2 Patient characteristics at enrolment

Patients enrolled	Sertindole group *n* (%) 1,064	Non-sertindole group *n* (%) 1,257
Sex		
Male	570 (54)	755 (60)
Female	494 (46)	502 (40)
Race		
Caucasian	1,014 (95)	1,198 (95)
Black	22 (2)	27 (2)
Asian	20 (2)	23 (2)
Other	8 (1)	9 (1)
Age		
Mean (range)	39 years (14–88 years)	42 years (17–90 years)
18–44 years	755 (71)	767 (61)
45–64 years	245 (23)	392 (31)
History of psychiatric illness		
Schizophrenia as primary psychiatric illness	1,013 (95)	1,205 (96)
First episode of schizophrenia	176 (17)	137 (11)
Duration of schizophrenia >10 years	391 (37)	660 (53)
Mild schizophrenia, CGI measurement	167 (16)	268 (21)
Moderate schizophrenia, CGI measurement	613 (58)	679 (54)
Severe schizophrenia, CGI measurement	282 (27)	310 (25)
Hospitalized at enrolment (due to primary illness)	487 (46)	487 (39)
History of suicide attempts	250 (23%)	312 (25%)

In the sertindole group, 11 patients did not take sertindole during the observation period. The reasons for this included abnormal baseline ECGs and withdrawal of consent prior to treatment. All 11 patients were nevertheless included in the safety analysis. Thirty-four patients were enrolled prior to the date on the consent form, but were included in the safety analysis. Sixteen patients in the sertindole group also started sertindole treatment more than 7 days (8–73 days) before enrolment, and 21 patients began 1–7 days before enrolment. All 37 were included in the safety analysis. A total of 145 patients in the sertindole group and 528 non-sertindole patients did not have an ECG recording before enrolment, but they were all included in their respective groups.

Table 3 Concurrent illnesses

	Sertindole group *n* (%)	Non-sertindole group *n* (%)
Patients reporting concurrent illness	351 (33)	425 (34)
Endocrine, nutritional, and metabolic diseases	101 (9)	103 (8)
Diabetes mellitus	31	
Hypothyroidism	23	
Obesity	20	
Hyperfunction of pituitary gland	11	
Lipidaemias	8	
Cardiovascular diseases	68 (6)	98 (8)
Previous history of cardiovascular disease	22 (2)	31 (2)
Hypertensive disease	35	51
Ischaemic disease	8	12
Chronic rheumatic heart disease		3
Pulmonary heart disease		1
Other forms of heart diseases	14	22
Diseases of the arterial and capillary system		5
Other unspecified circulatory disorder	7	6
Cerebrovascular diseases	3	1
Diseases of the veins, lymphatic vessels, and lymph nodes	4	10
Nervous system diseases	51 (5)	79 (6)

Safety

Ten patients in the sertindole group, and nine patients in the non-sertindole group, died during the study, but 11 and 10 SAEs with a fatal outcome, respectively, were recorded in the safety database. In the sertindole group, the discrepancy occurred because one patient died 2 months after withdrawing consent to participate and being withdrawn from the study; in the non-sertindole group, one patient died 3 months after completing the study.

Deaths

Crude mortality rates in the sertindole and the non-sertindole groups are shown in Table 4. The deaths have been categorized by cause into non-cardiac, cardiac, uncertain cause, and suicide. Six patients died from SAEs that occurred within the period up to 5 days after discontinuing sertindole and a further five patients died from SAEs that occurred more than 5 days after stopping sertindole treatment; ten deaths occurred in the non-sertindole group.

Suicide was the most common cause of death in the sertindole group, with three completed suicides (judged to be unrelated to sertindole treatment) occurring from start of treatment up to 5 days after discontinuation. Non-cardiac death was the most common cause of death in the non-sertindole group. In the sertindole group, no fatal cardiac AEs occurred within the study period or 5 days of cessation of sertindole treatment. With respect to age, five of the six sertindole patients who died from SAEs that occurred within the study period or in the 5 days after discontinuing sertindole were 45 years of age or younger, and seven of the ten non-sertindole patients were 45 years of age or older.

Of the six SAEs that occurred within the period up to 5 days of stopping treatment with sertindole, the relationship to treatment was not assessable in one case because insufficient information was available to judge the case. The remaining five deaths were judged not to be related to sertindole treatment.

Of the five patients who died from SAEs that occurred more than 5 days after the end of sertindole treatment, all but one had been switched to another sequential antipsychotic treatment, and the relationship to sertindole treatment was assessed as non-related. The one known cardiac death in this group occurred in a patient who had a myocardial infarction (MI) but he had a family history of MI at a young age and was both obese and a heavy smoker. Moreover, this patient stopped sertindole treatment 2–3 weeks prior to death and was taking a combination of three other antipsychotics at the time of death.

In the non-sertindole group, one death was judged to be probably related to antipsychotic treatment (haloperidol and flupenthixol)—death occurred in an 81-year-old man who died from bronchopneumonia and chronic obstructive pulmonary disease. The remaining nine deaths were judged to be unrelated to antipsychotic treatment.

Other serious adverse events

Including deaths, there were 67 SAEs in the sertindole group (57 patients) during sertindole treatment. They affected many body systems. Fifteen of the SAEs were considered 'related' to sertindole—that is, they were either assessed to be 'possibly' or 'probably' related to sertindole or the relationship to treatment could not be assessed or was missing (Table 5). Of these 15 'related' SAEs, 8 affected the nervous system. Table 6 lists the SAEs that were 'not related' to sertindole treatment. A further 26 SAEs were reported by 22 patients after they had stopped taking sertindole—one, a non-fatal overdose of levomepromazine, occurred 2 days after discontinuation, and the other 25 events occurred between 1 week and 8 months after discontinuation.

Of the cardiac AEs in the sertindole group, only one was related to an abnormal ECG. However, this was later judged

Table 4 Crude mortality rates for the sertindole ($n = 1{,}053$) and non-sertindole groups ($n = 1{,}257$)

	Sertindole group	Non-sertindole group	Crude mortality/100 PYE (95% CI)	
			Sertindole group	Non-sertindole group
PYE	414	667		
All deaths	6 (4 males/2 females)	10 (8 males/2 females)	1.45 (0.53–3.16)	1.50 (0.72–2.76)
All deaths except suicides	3	9	0.73 (0.15–2.12)	1.35 (0.62–2.56)
Non-cardiac	1	8	0.24 (0.01–1.35)	1.20 (0.52–2.36)
Cardiac	0	1	0	0.15 (0.00–0.84)
Uncertain cause	2	0	0.48 (0.06–1.75)	0
Suicide	3	1	0.73 (0.15–2.12)	0.15 (0.00–0.84)

PYE patient-years of exposure, *CI* confidence interval

Table 5 'Related' serious adverse events (SAEs), including deaths, that occurred during sertindole and non-sertindole treatment

Body system	COSTART[a] term	Sertindole group (*n*)	Non-sertindole group (*n*)
Body as a whole	Cyst		1
	Death	1[b]	
	Injury accidental		1[b]
	Overdose		2
	Overdose accidental		1
	Shock		2
	Suicide attempt	2	
Cardiovascular system	Bradycardia	1	
	Extrasystoles ventricular		1
	Infarct myocardial	1	
	Sinus tachycardia		1
Cerebrovascular system	Ischaemia cerebral		1
Digestive system	Gastritis	1	
	Ileus		1
Metabolic/nutritional disorders	Liver function abnormal	1	
Blood/lymphatic system	Agranulocytosis		1
Respiratory system	Pneumonia		2
Nervous system	Convulsions	1	
	Convulsions grand mal	1	
	Depression	3	
	Insomnia	2	
	Psychosis	1	
Total		15	14

'Related' refers to the causality of the SAE being assessed as 'probable', 'possible', 'not assessable' or causality assessment missing, with respect to the sertindole/non-sertindole treatment received

[a] COSTART is the Food and Drug Administration's Coding Symbols for a Thesaurus of Adverse Reactions

[b] Outcome death

by a cardiologist to be an artefact. Two patients also experienced cardiac arrhythmias: one with atrial fibrillation and one with episodic bradycardia, syncope, and QT interval prolongation. In the case of the first patient, atrial fibrillation was present both before and after the sertindole treatment period. In the second case, however, a 41-year-old woman gained weight and was later found to have sleep apnoea and a widely varying heart rate. The investigator assessed that the AE was probably related to sertindole treatment.

There were two cases of MI in the sertindole group, one in a 56-year-old man with multiple cardiac risk factors and the second in an 83-year-old woman with a 4-year history of heart disease. In the first case, the onset of chest pain occurred 4 months after the start of sertindole treatment and it was rated to be possibly related to the treatment. Two cases of syncope occurred, although in one of the cases no clear signs of syncope were observed. In this case, the patient needed no medical treatment or a pacemaker and the dose of sertindole was increased 6 weeks after the incident without any similar AEs. In the other case, the patient had a history of syncope and reported two more episodes after stopping sertindole treatment.

Two patients had convulsions during sertindole treatment. However, one of these patients had a prior history of

Table 6 'Not related' serious adverse events (SAEs), including deaths, that occurred during sertindole and non-sertindole treatment

Body system	COSTART[a] term	Sertindole group (*n*)	Non-sertindole group (*n*)
Body as a whole	Carcinoma thyroid		1
	Cyst	1	
	Death	1[b]	
	Fever	1	
	Hypothermia		1
	Infection	2	
	Injury accidental	3 (1[b])	5 (1[b])
	Injury intentional		1[b]
	Overdose	5	6
	Overdose intentional	2	
	Pain	1	
	Pain abdominal	1	1
	Pain chest		1
	Sepsis		3 (2[b])
	Suicide attempt	10 (3[b])	5 (1[b])
Cardiovascular system	Angina pectoris	1	
	Anomaly vascular		1
	ECG abnormal	1	
	Embolus pulmonary	1	1
	Fibrillation atrial	1	
	Hypotension		1
	Infarct myocardial	1	1[b]
	Ischaemia myocardial		1
	Oedema (legs)		1
	Syncope	2	
Cerebrovascular system	Ischaemia cerebral		1
Digestive system	Cholecystitis	1	
	GI disorder	1	
	Haematemesis	3 (one patient)	
	Haemorrhage rectal	1	
	Intestinal perforation	1	
	Nausea	1	
	Ulcer duodenal haemorrhage	1	
Metabolic/nutritional disorders	Alcohol intolerance		1
	Hyponatraemia		1
Blood/lymphatic system	Hypochromic anaemia		1
	Lymphoma-like reaction		1
	Thrombocytopenia	1	
Musculoskeletal system	Bone disorder		1
	Bone fracture spontaneous		1
	Tendon rupture		1
	Tenosynovitis		1
Respiratory system	Bronchitis		2 (one patient)
	Carcinoma lung		1[b]
	Epistaxis	1	1
	Lung disorder		3 (two patients)
	Pleural disorder		1
	Pneumonia	3	2 (1[b])
	Respiratory disorder		1[b]

Table 6 continued

Body system	COSTART[a] term	Sertindole group (*n*)	Non-sertindole group (*n*)
Special senses	Glaucoma		1
	Retinal detachment	1	
Skin	Skin benign neoplasm		1
Nervous system	Abnormal gait	2	
	Anxiety		1
	Convulsions		1
	Depression		1
	Drug dependence	1	
Urogenital system	Cystitis		1
	Haematuria		1
	Pregnancy disorder		1
Total		52	58

'Not related' SAEs were those that were judged not to be related to the sertindole/non-sertindole treatment received

[a] COSTART is the Food and Drug Administration's Coding Symbols for a Thesaurus of Adverse Reactions

[b] Indicates the number of death outcomes

convulsions and had stopped taking anti-epileptic treatment. The second patient had not previously experienced seizures and, on investigation, EEG revealed disturbances considered related to treatment with perazine.

SAEs that occurred in the non-sertindole group are also summarized in Tables 5 and 6. Seventy-two SAEs, including deaths, were reported for 59 patients. Fourteen events were judged to be 'related' to antipsychotic treatment—that is, they were assessed to be 'possibly' or 'probably' related to antipsychotic treatment, or the relationship was not assessable or was missing. Of those unrelated to treatment, nine were fatal. Like the SAEs that occurred in the sertindole group, those that occurred in the non-sertindole group affected several different body systems. The number of cardiac SAEs related to treatment in this group was similar to that in the sertindole group. A case of asymptomatic ventricular extrasystole in a 33-year-old man was thought to be related to pimozide treatment. Another young man (28 years old) had chest pain and the ECG revealed sinus tachycardia and ventricular extrasystole. He had a history of heartbeat abnormalities, although this event was judged to be possibly related to clozapine treatment. The third case was one of fatal MI.

QT interval prolongation

No ventricular tachyarrhythmias—the possible consequence of QT interval prolongation—were recorded in the sertindole group [13, 14]. There were, however, cases of syncopes and convulsions, as reported above. Since both syncope and convulsions could be symptoms of a short-lasting cardiac arrhythmia, these events are of particular interest. Potential symptoms of arrhythmia experienced during sertindole treatment and the observation period for patients in the non-sertindole group are considered in Table 7.

Table 7 Number of patients with adverse events (all intensities) that might be related to cardiac arrhythmias during treatment with sertindole or during the observation period (non-sertindole group)

Adverse event	Sertindole ($n = 1{,}053$)	Non-sertindole ($n = 1{,}257$)
Syncope	9	4
Convulsion	4	7
Convulsion grand mal	2	1
Cardiac death	0	1
Death of uncertain aetiology	2	0
Total	17	12[a]

[a] One patient in the non-sertindole group had both a convulsion and a grand mal

Of the six sertindole patients who had convulsions or grand mal convulsions during treatment, one had a prolonged QT_C interval, although it did not exceed 500 ms (476 ms). Similarly, of the eight patients with convulsions or grand mal convulsions in the non-sertindole group, one had a prolonged QT_C interval at one ECG (512 ms), although several repeat tests did not confirm the prolongation. Moreover, the patient was severely ill with sepsis. A second patient had one normal ECG and one that suggested borderline QT_C interval prolongation. This patient was later treated with sertindole, during which time another ECG revealed QT_C interval prolongation (461 ms).

One of the nine patients who experienced syncope during sertindole treatment had a normal baseline QT_C interval, but a second ECG before the event occurred

suggested QT_C interval prolongation (475 ms). This patient continued taking sertindole without any further episodes of syncope. In the non-sertindole group, four patients experienced syncope, one had a prolonged QT_C interval at baseline (457 ms). Two of these patients were shown to have QT_C interval prolongation after the event and the other two had borderline-prolonged values.

The two sertindole-treated patients whose cause of death was uncertain both had normal QT_C interval values at enrolment, although one had atrial fibrillation and left ventricular hypertrophy. Similarly, the patient whose death was classified as 'cardiac death' in the non-sertindole group also had a normal ECG at baseline.

Other adverse events

During the first 4 weeks of sertindole treatment 650 (62%) of the 1,050 patients remaining in the cohort (some patients withdrew informed consent shortly after enrolment) experienced at least one AE. However, the prevalence of AEs generally decreased with time. In particular, AEs that affected the nervous system, the body as a whole, and the digestive system decreased with time, while those affecting the blood, lymphatic, musculoskeletal, skin and appendages, and endocrine systems remained stable. After 4 weeks, a slight increase was observed in the number of metabolic and nutritional disorder AEs. EPS increased slightly in the first 4 weeks of sertindole treatment but then fell back to below baseline levels. ECG monitoring was mandatory between 85 and 180 days of treatment and 2% of the patients had QT interval prolongation.

Most AEs in the sertindole group each occurred in only a small number of patients. Those that occurred in 5% or more of the patients during the first 4 weeks of treatment were: ejaculation abnormal (7%), akathisia (7%), weight increase (6%), hypertonia (6%), rhinitis (6%), headache (5%), tremor (5%).

In the non-sertindole group, 621 (51%) of the 1,224 patients remaining in the cohort experienced at least one AE during the first 4 weeks of the observation period. During the study, small increases in the number of AEs that affected the nervous and digestive systems were observed, although the overall frequency of AEs remained the same. EPS were reported by 183 (15%) patients at enrolment and the proportion of patients with EPS rose slightly to 18% during the study. Only tremor occurred in 6% of the patients.

Discussion

The post-marketing EPOS study was proposed to assess the safety profile of sertindole in real-life clinical practice, and to gather additional data on the treatment of schizophrenia. However, due to the early termination of the study, only a small proportion of the planned number of patients was enrolled and the power of the study was considerably weakened. The information gathered is nevertheless still of interest, and may be useful in future meta-analysis, provided certain considerations are taken into account.

The study had an effectiveness design. The reference arm was designed to have two times as many patients as the sertindole group, and the groups were not expected to be comparable due to different selection criteria.

In the end, the sample size was close for both groups. The population studied displayed modest disproportionality in gender, drug history, and illness severity. The sertindole group in general consisted of younger patients during an unstable period of their illness, which tended to be moderate to severe. The non-sertindole group profile was more stable, the majority of patients having been ill for over 10 years, and they were more likely to have mild schizophrenia.

Suicide was the most common cause of death in the sertindole group. Montross and Kasckow have noted that patients with schizophrenia are at a high risk of suicide in the early years following their diagnosis, and are in addition especially at risk in the period just following hospital discharge [14]. In comparison with the non-sertindole group, the sertindole group had higher percentages of patients experiencing their first episode of schizophrenia, of those hospitalized at enrolment, and of those whose duration of schizophrenia was less than 10 years. Thus, more suicide would have been expected in the sertindole group. In fact, there were very small numbers of suicides, three in the sertindole group and one in the non-sertindole group. Montout et al. report a suicide rate in patients with schizophrenia of about 0.7% over a 1-year period; in the sertindole group, this was about 0.28% over a 1-year period, lower than that which would therefore have been expected [15].

It should be noted that this study was firmly based in real-life clinical practice. Physicians treating a patient with a cardiac risk profile, and who are aware of the potential cardiac effects of sertindole, would chose to prescribe an alternative drug. This channelling by indication effect changed the profile of the sertindole group and would have had the effect of decreasing the amount of cardiac events in this group. It is also known that older, male patients are more likely to have cardiac problems. As the percentage of males in the sertindole group was 54% as opposed to 60% in the non-sertindole group, it is possible that this too decreased the relative amounts of cardiac events seen in the sertindole group.

Due to the differences in patients' profiles, the higher rate of suicide and lower rate of cardiac death in the

sertindole cohort are not unexpected. Unfortunately the differences between the two cohorts render the interpretation of those results difficult. In addition, the fact that 11 patients in the sertindole group did not receive sertindole yet were kept in the analysis introduces a bias in favour of sertindole. However, nine patients in the non-sertindole group, similarly retained in the analysis, did not receive any medication, which could have biased the results in this group's favour. Interpretation is further complicated by the retention of patients who did not have a primary diagnosis of schizophrenia (50 in the sertindole group and 52 in the non-sertindole group); these patients may have had different side effect profiles compared with the patients with schizophrenia.

However, in spite of these reservations concerning the interpretation of the results, in this study patient exposure was high, reaching levels not far from that used for registration of a new compound. It would therefore seem reasonable to conclude that sertindole does not present a high risk of serious cardiac events when used in current clinical practice. Sertindole was generally well tolerated and the tolerability profile was similar to that observed in other studies [3, 4, 6–8]. Troublesome AEs, such as EPS, were few and when they did occur, tended to decline in severity within a short period. The death rates observed were consistent or lower in this observational study compared to that observed in the clinical trials. This might be explained by the more stringent inclusion criteria in routine practice in relation to the warning and contra-indications seen in the sertindole SPC [12].

The study does not suggest evidence of excess risk of mortality associated with the use of sertindole.

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