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# Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data

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## Abstract

**Objective** To examine the rates of cardiac arrest and ventricular arrhythmia in patients with treated schizophrenia and in non-schizophrenic controls.

**Design** Cohort study of outpatients using administrative data.

**Setting** 3 US Medicaid programmes.

**Participants** Patients with schizophrenia treated with clozapine, haloperidol, risperidone, or thioridazine; a control group of patients with glaucoma; and a control group of patients with psoriasis.

**Main outcome measure** Diagnosis of cardiac arrest or ventricular arrhythmia.

**Results** Patients with treated schizophrenia had higher rates of cardiac arrest and ventricular arrhythmia than controls, with rate ratios ranging from 1.7 to 3.2.

Overall, thioridazine was not associated with an increased risk compared with haloperidol (rate ratio 0.9, 95% confidence interval 0.7 to 1.2). However, thioridazine showed an increased risk of events at doses  $\geq 600$  mg (2.6, 1.0 to 6.6;  $P=0.049$ ) and a linear dose-response relation ( $P=0.038$ ).

**Conclusions** The increased risk of cardiac arrest and ventricular arrhythmia in patients with treated schizophrenia could be due to the disease or its treatment. Overall, the risk with thioridazine was no worse than that with haloperidol. Thioridazine may, however, have a higher risk at high doses, although this finding could be due to chance. To reduce cardiac risk, thioridazine should be prescribed at the lowest dose needed to obtain an optimal therapeutic effect.

## Introduction

Many antipsychotic drugs can prolong the QT interval, and many have been linked to cases of torsade de pointes.<sup>1</sup> Haloperidol and thioridazine are the most widely used typical antipsychotic drugs in the United States.<sup>2</sup> Cross sectional data suggest that thioridazine may prolong the QT interval more than haloperidol,<sup>3</sup> although only one experimental study has compared the QT effects of these drugs in humans.<sup>4</sup> The clinical importance of QT interval prolongation is not known.

We compared the frequency of cardiac arrest and ventricular arrhythmia associated with different antipsychotic drugs, in particular comparing thioridazine to haloperidol. Because cases of ventricular arrhythmia and cardiac arrest may go undiagnosed, we also examined deaths from all causes.

## Participants and methods

### Overview and study population

We conducted a cohort study of outpatients by using 1993 to 1996 data from three US Medicaid

programmes.<sup>5</sup> We identified individuals with more than one prescription for oral thioridazine, haloperidol, risperidone, or clozapine plus at least two instances of a schizophrenia diagnosis.

For each prescription, patients were followed until the end of the prescription duration, appearance of an intervening prescription for the same or a different study drug, or occurrence of the study outcome, whichever came first. Prescriptions for multiple study drugs dispensed on the same day were excluded.

We identified two control groups based on a diagnosis of open angle glaucoma or psoriasis. These conditions were selected because they require periodic prescriptions and are not thought to be associated with cardiovascular outcomes.<sup>6,7</sup> We followed controls from the first diagnosis of the reference condition until the occurrence of the study outcome or the last claim, whichever came first.

### Study outcomes

The primary outcome was sudden death and ventricular arrhythmia (see [bmj.com](http://bmj.com)). In studying all cause death, we first identified "potential deaths" among patients taking antipsychotic drugs as instances in which there were no claims after the end of the last prescription. For the control groups, potential deaths were instances in which claims stopped 90 days or more before the end of the data availability period.

### Analysis

We calculated rate ratios and 95% confidence intervals using proportional hazards regression. For each outcome, we constructed three sets of models. The first set included patients taking antipsychotic drugs plus glaucoma patients, using glaucoma as the reference. The second set included patients taking antipsychotic drugs plus psoriasis patients, using psoriasis as the reference. The third set included only patients taking antipsychotic drugs and used haloperidol as the reference. We first adjusted for state, sex, and age. We then individually examined year, drug exposures, and diagnoses as potential confounders (see [bmj.com](http://bmj.com)). We conducted an analysis of high risk patients, defined as those with diagnosed heart disease or a current prescription for an antiarrhythmic drug, loop diuretic, cisapride, terfenadine, amitriptyline, or pindolol. We also separately examined patients aged 65 and older and women.<sup>8</sup>

We calculated the average daily dose for each patient, for each drug, by dividing the total quantity of drug dispensed by the duration of observation. We examined the effect of dose on the primary outcome in two ways. Firstly, we performed subanalyses of those receiving  $< 100$  mg, 100-299.9 mg, 300-599.9 mg, and  $\geq 600$  mg/day in thioridazine equivalents. We consid-

**Table 1** Age, sex, and crude and standardised rates of cardiac arrest and ventricular arrhythmia and all cause mortality according to drug taken

	Clozapine (n=8330)	Haloperidol (n=41 295)	Risperidone (n=22 057)	Thioridazine (n=23 950)	Psoriasis drug (n=7541)	Glaucoma drug (n=21 545)
No (%) of women:	3370 (40)	20 913 (51)	10 621 (48)	12 916 (54)	4 460 (59)	15 609 (72)
No (%) aged (years):						
≤34	3131 (38)	12 422 (30)	7 243 (33)	6 890 (29)	2 806 (37)	773 (4)
35-44	2878 (35)	10 338 (25)	6 673 (30)	5 659 (24)	1 328 (18)	856 (4)
45-54	1304 (16)	6 471 (16)	3 827 (17)	4 185 (17)	1 051 (14)	1 876 (9)
55-64	631 (8)	4 984 (12)	2 171 (10)	3 260 (14)	1 075 (14)	3 962 (18)
65-74	306 (4)	3 786 (9)	1 412 (6)	2 361 (10)	705 (9)	6 344 (29)
≥75	80 (1)	3 294 (8)	731 (3)	1 595 (7)	576 (8)	7 734 (36)
Cardiac arrest and ventricular arrhythmia:						
Person years of observation	8821	31 911	10 181	22 378	11 015	35 062
No of cases	19	135	51	86	20	119
Rate per 1000 person years (95% CI)	2.2 (1.3 to 3.4)	4.2 (3.5 to 5.0)	5.0 (3.7 to 6.6)	3.8 (3.0 to 4.7)	1.8 (1.1 to 2.8)	3.4 (2.8 to 4.1)
All cause mortality:						
Person years of observation	8829	32 088	10 250	22 455	11 045	35 144
No of cases	24	235	74	146	30	138
Rate per 1000 person years (95% CI)	2.7 (1.7 to 4.0)	7.3 (6.4 to 8.3)	7.2 (5.7 to 9.1)	6.5 (5.5 to 7.6)	2.7 (1.8 to 3.9)	3.9 (3.3 to 4.6)

**Table 2** Adjusted\* rate ratios and 95% confidence intervals for cardiac arrest and ventricular arrhythmia and all cause mortality in patients taking antipsychotic drugs with glaucoma patients, psoriasis patients, or patients taking haloperidol as the reference category

Drug	Cardiac arrest and ventricular arrhythmia			Death		
	Glaucoma	Psoriasis	Haloperidol	Glaucoma	Psoriasis	Haloperidol
Clozapine	1.7 (1.0 to 2.9)	1.9 (1.0 to 3.7)	0.7 (0.4 to 1.2)	3.4 (2.1 to 5.5)	2.6 (1.5 to 4.5)	0.8 (0.5 to 1.2)
Haloperidol	2.2 (1.7 to 3.0)	2.4 (1.5 to 3.9)	1.0 (reference)	4.5 (3.6 to 5.7)	3.2 (2.2 to 4.8)	1.0 (reference)
Risperidone	3.1 (2.2 to 4.5)	3.2 (1.9 to 5.4)	1.5 (1.1 to 2.1)	5.8 (4.3 to 8.0)	4.1 (2.7 to 6.4)	1.4 (1.1 to 1.9)
Thioridazine	2.2 (1.6 to 3.0)	2.4 (1.4 to 3.9)	0.9 (0.7 to 1.2)	4.0 (3.1 to 5.2)	2.9 (2.0 to 4.4)	0.8 (0.7 to 1.0)

\*see bmj.com for a detailed list of covariates for which rates were adjusted.

ered 2.5 mg haloperidol, 50 mg clozapine, and 0.75 mg risperidone equivalent to 100 mg thioridazine.<sup>9</sup> Secondly, we did a subanalysis for each drug separately, looking at the rate ratio for each quarter versus the lowest quarter and calculating a P value for a linear trend using the median in each quarter as the exposure level.<sup>10</sup> We examined confounders in the same way described above.

## Results

The antipsychotic and psoriasis groups had similar ages, but the glaucoma group was older (table 1).

Potential confounders did not affect the rate ratios of interest in analyses restricted to patients taking antipsychotic drugs but did confound the comparisons with non-schizophrenic patients (table 2). Compared to the glaucoma and psoriasis control groups, patients taking antipsychotic drugs had rate ratios for cardiac arrest and ventricular arrhythmia ranging from 1.7 to 3.2, and those for death ranged from 2.6 to 5.8.

Risperidone was the only drug that had higher rates than haloperidol for cardiac arrest and ventricu-

lar arrhythmia and for death. Overall, thioridazine was not associated with an increased rate of cardiac arrest and ventricular arrhythmia or death compared with haloperidol (table 2).

Thioridazine was also not associated with a higher rate of cardiac arrest and ventricular arrhythmia than haloperidol in the high risk population (1.1, 0.8 to 1.7), among those aged ≥65 years (0.9, 0.6 to 1.4), or in women (1.1, 0.7 to 1.6). The dose specific rate ratio for cardiac arrest and ventricular arrhythmia for thioridazine versus haloperidol was 0.6 (0.3 to 1.0) for <100 mg/day in thioridazine equivalents; 1.2 (0.8 to 1.9) for 100-299.9 mg/day; 1.1 (0.6 to 2.0) for 300-599.9 mg per day; and 2.6 (1.0 to 6.6; P=0.049) for ≥600 mg/day.

Compared with thioridazine, haloperidol was used at roughly three times the equivalent dose (table 3). A dose-response relation was apparent for thioridazine (P=0.038), with patients in the highest quarter having a rate ratio of 2.5 (1.1 to 5.4) relative to those in the lowest quarter. For risperidone, the highest risk occurred with the lowest dose.

**Table 3** Rate ratios for cardiac arrest and ventricular arrhythmia according to dose quarters of study drugs

Quarter	Clozapine		Haloperidol		Risperidone		Thioridazine	
	Average daily dose (mg)*	Rate ratio (95% CI)†	Average daily dose (mg)*	Rate ratio (95% CI)‡	Average daily dose (mg)*	Rate ratio (95% CI)†	Average daily dose (mg)*	Rate ratio (95% CI)†§
1	<243 (<486)	1.0 (reference)	<3.5 (<140)	1.0 (reference)	<2.8 (<420)	1.0 (reference)	<51 mg (<51)	1.0 (reference)
2	243-385 (486-770)	3.4 (0.8 to 14.6)	3.5-7.5 (140-300)	0.6 (0.3 to 1.0)	2.8-5.0 (420-750)	0.6 (0.3 to 1.3)	51-102 (51-102)	1.6 (0.7 to 3.6)
3	386-543 (772-1086)	1.3 (0.2 to 7.1)	7.6-15.0 (304-600)	0.9 (0.6 to 1.5)	5.1-6.5 (765-975)	0.4 (0.2 to 1.0)	103-204 (103-204)	2.2 (1.0 to 4.8)
4	>543 (>1086)	0.6 (0.1 to 4.6)	>15.0 (>600)	1.0 (0.6 to 1.7)	>6.5 (>975)	0.7 (0.3 to 1.4)	>204 (>204)	2.5 (1.1 to 5.4)

\*Approximate equivalent dose of thioridazine given in parentheses.

†Adjusted for age, sex, state, and current use of an inotropic drug.

‡Adjusted for age, sex, and state.

§P=0.038 for linear dose-response relation.

## Discussion

### Differential effects of antipsychotic drugs

The rate ratio for cardiac arrest and ventricular arrhythmia for risperidone compared with haloperidol was 1.5 (1.1 to 2.1). In a study comparing QT effects of different antipsychotics, risperidone 16 mg/day had an average QT effect similar to that shown by haloperidol 15 mg/day.<sup>4</sup> We therefore did not expect that risperidone would have a greater effect than haloperidol. The fact that the highest rate was seen with the lowest risperidone dose also argues against a causal interpretation. One potential explanation is that risperidone was used preferentially, and at low dose, in the frailest patients,<sup>11</sup> who were at highest risk. Therefore, we report this result as an incidental finding to be examined in future research.

We found that thioridazine had no higher risk of cardiac events than haloperidol. However, our data suggest that at high doses thioridazine may have a higher risk than haloperidol and that there may be a dose-response relation for thioridazine. These findings had marginal P values and arose from multiple comparisons. However, they support the recent finding that at >100 mg/day, the rate ratio for thioridazine versus haloperidol was 1.7,<sup>8</sup> and the finding that arrhythmia was more common in patients with thioridazine than haloperidol overdoses.<sup>12</sup> Taken together, these findings suggest that at high dose, thioridazine may be worse than haloperidol. Thus, to minimise the risk of arrhythmia it seems prudent to prescribe the lowest dose of thioridazine possible.

### Limitations

Although privacy concerns prevented review of medical records, we used a previously validated outcome.<sup>13</sup> We could not specifically study torsade de pointes, the arrhythmia of greatest interest, although we did study the clinically important consequences of torsade. We attempted to limit confounding by indication by excluding non-schizophrenic patients from the exposed groups and by examining a large number of clinical variables as potential confounding factors. However, confounding by indication may still have occurred, and we believe it may account for the risperidone results. Finally, because we studied patients taking oral drugs, the results may not be generalisable to patients receiving parenteral therapy.

In conclusion, our findings indicate that use of antipsychotic drugs among patients with schizophrenia is associated with increased rates of cardiac arrest and ventricular arrhythmia and of death. Patients taking high doses of thioridazine may be at higher risk than those taking equivalent doses of haloperidol. To reduce the risk of arrhythmia, patients requiring thioridazine should be given the lowest dose needed to obtain an optimal therapeutic effect.

Contributors: see bmj.com

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## What is already known on this topic

Thioridazine seems to prolong the electrocardiographic QT interval more than haloperidol

Although QT prolongation is used as a marker of arrhythmogenicity, it is unknown whether thioridazine is any worse than haloperidol with regard to cardiac safety

## What this study adds

Patients taking antipsychotic drugs had higher risks of cardiac events than control patients with glaucoma or psoriasis

Overall, the risk of cardiac arrest and ventricular arrhythmia was not higher with thioridazine than haloperidol

Thioridazine may carry a greater risk than haloperidol at high doses

Patients should be treated with the lowest dose of thioridazine needed to treat their symptoms

McNeil, and Janssen. SEK has received research funding from Pfizer, Novartis, and McNeil.

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## Endpiece

### Less than a hair's breadth away

Disorder and abjection stand less than a hair's breadth away from every human creature.

Robertson Davies (1913-95), *What's bred in the bone*, London: Penguin, 1986