

**FDA Background  
On**

**Zeldox™ (ziprasidone hydrochloride capsules)  
Pfizer, Inc.**

**Psychopharmacological Drugs Advisory Committee**

**July 19, 2000**

Holiday Inn, Versailles Ballroom I-III  
8120 Wisconsin Avenue, Bethesda, Maryland

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# Overview Memo



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**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH****DATE:** June 20, 2000**FROM:** Thomas P. Laughren, M.D. *Thomas P. Laughren*  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120**SUBJECT:** July 19, 2000 Meeting of the Psychopharmacological Drugs Advisory Committee (PDAC)**TO:** Psychopharmacological Drugs Advisory Committee (PDAC)

NDA 20-825 for ziprasidone in the treatment of schizophrenia was originally submitted March 18, 1997. A not-approvable letter was issued to Pfizer for this NDA on June 17, 1998, based on "the judgement that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular arrhythmias that is not outweighed by a demonstrated and sufficient advantage of ziprasidone over already marketed antipsychotic drug products." This judgement was based on a finding in the short-term, fixed dose, placebo-controlled phase 2/3 studies of a dose-related tendency for ziprasidone to increase the QTc. The size of the QTc increase compared to placebo was about 10 msec at the 160 mg/day dose. In addition, we raised the concern that the 10 msec increase observed may have represented an underestimate, given the fact that most ECGs were likely obtained at trough ziprasidone plasma levels, and Cmax plasma levels might be expected to be at least double those seen at trough. The June 17, 1998 letter expressed the view that the size of the QTc increase is a factor in determining the degree of risk of ventricular arrhythmias, and further, suggested that "we would find QTc prolongation at maximum blood levels in the 5-10 msec range, with adequate assurances that there are very few outliers and that there are no factors that lead to substantially greater values in individuals (such as drug-drug interactions) sufficiently reassuring, in the absence of contrary evidence, to support approval of a new antipsychotic such as ziprasidone." The letter recommended further study to determine the QTc effect of ziprasidone at peak plasma concentrations, in comparison with other atypical antipsychotics and with several standard antipsychotics.

Pfizer has since conducted Study 054, a head-to-head safety comparison of ziprasidone at its optimal dose with several other antipsychotics at their optimal doses (haloperidol, thioridazine, olanzapine, risperidone, and quetiapine), with ECGs obtained at estimated Tmax for each of these drugs. This study also included a phase adding a metabolic inhibitor for each of these drugs to determine the

additive effects on QTc of what would be expected to be maximal inhibition of the clearance of each of these drugs.

In summarizing the results of study 054, Pfizer has stated that this study reveals an effect on QTc prolongation approximately 10 msec greater than that observed with 4 of the comparison drugs (i.e., haloperidol, olanzapine, risperidone, and quetiapine), and an effect on QTc prolongation approximately 10 msec less than that observed with thioridazine. We are in agreement with Pfizer on this finding of the relative placement of ziprasidone vs the other drugs in this study, i.e., a QTc prolongation 10 msec greater for ziprasidone compared to these 4 drugs and a 10 msec lesser effect compared to thioridazine. Regarding the increases from baseline observed for the other drugs in study 054, it is not clear, in our view, whether the observed QTc increases represent actual drug-related effects or represent placebo effect, since we have an abundance of data from multiple independent development programs showing no difference between haloperidol (at the oral dose used in study 054) and placebo on QTc.

We are also in general agreement with Pfizer on the antipsychotic efficacy of ziprasidone based on the short-term, fixed dose, placebo-controlled phase 2/3 studies. Of note, however, we are not aware of any evidence from these or any other studies of any superior antipsychotic efficacy for ziprasidone compared to any other antipsychotic drugs, either in typical schizophrenic patients or in those shown refractory to standard antipsychotic therapy.

The planned program for the July 19th meeting will begin with presentations by Pfizer of the overall antipsychotic efficacy and safety of ziprasidone, with a particular emphasis on the findings pertinent to QTc prolongation. FDA presentations will follow, and will also focus on the issue of QTc prolongation and risk of ventricular arrhythmias. These presentations will include data and discussions regarding other drugs with findings pertinent to the issue of QTc prolongation, such as terfenadine, sertindole, thioridazine, and the quinolones. An update will be provided on a labeling change recently implemented for the drug thioridazine.

The general questions for the committee will focus on the safety and efficacy of ziprasidone for the treatment of schizophrenia. In particular, the critical safety question will be the relevance of the 10 msec prolongation of the QTc observed for ziprasidone, and not for several other antipsychotic drugs included in study 054, for the approvability of this drug.

Besides this memo, FDA's package for this meeting includes a draft review of study 054 from the Division of Cardio-Renal Drug Products. This draft review reaches a conclusion that ziprasidone's greater QTc prolongation effect than observed with a number of other antipsychotic drugs is predictive of a greater risk of potentially fatal ventricular arrhythmias for ziprasidone compared to these other drugs, and that this greater risk should, in the absence of a demonstration of some other greater benefit of ziprasidone compared to these other drugs, lead to either the non-approval of ziprasidone or a second line status for this drug. It is important to note that the Division of Neuropharmacological Drug Products and ODE-I have not yet reached a conclusion on this important question, and it is primarily for this reason that we have scheduled this meeting.

**cc:**

HFD-120/DivFile NDA 20-825 (ziprasidone)

HFD-120/TLaughren/RKatz/RGlass/SHardeman

**DOC:** PDAC0700.M01

Cardio Review

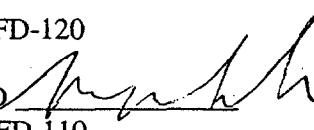


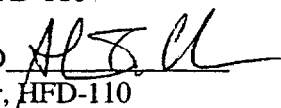
MEMORANDUM

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of CardioRenal Drug Products  
Consultation

Date: 6/14/00

To: Russell Katz, MD  
Division Director, HFD-120

From: Maryann Gordon, MD   
Medical Reviewer, HFD-110

Through: Shaw Chen, MD, PhD   
Medical Team Leader, HFD-110

Dr. Raymond Lipicky \_\_\_\_\_  
Division Director, HFD-110

Subject: Ziprasidone, NDA# 20825  
Study report of Clinical Pharmacology Protocol #128-054

Conclusion

Study 128-054 has demonstrated that the antipsychotic agents ziprasidone and thioridazine adversely affect cardiac repolarization in that these drugs prolong the QTc and QT intervals in a concentration-related manner. Patients who take drugs that prolong these ECG intervals are at risk of serious cardiac arrhythmias such as torsade de points (TdP) and sudden death. The effect on cardiac repolarization of the other antipsychotic agents used in study 128-054 for comparison appears to be minimal or absent.

Taking into account ECG data from this study as well as other trials, ziprasidone increases the QTc from baseline on average about 10-20 msec, thioridazine approximately 36 msec, and sertindole, an antipsychotic removed from the UK market for causing TdP and sudden death, about 21 msec. Although the magnitude of the increase of the QTc (and QT) is thought by experts to be important, it is not predictive of the degree of risk of TdP or other serious ventricular arrhythmias.

The co-administration of a metabolic inhibitor with ziprasidone and thioridazine increased blood levels and QTc only slightly compared to the use of these drugs alone. Therefore, drug-drug interactions similar to what occurred with terfenadine (when blood levels increased dramatically when ketoconazole was taken along with terfenadine) are much less of a concern with these agents.

In summary, a certain proportion of patients taking ziprasidone or thioridazine will have an increased risk of potentially fatal ventricular arrhythmias. The Cardio-Renal Division considers it essential that any agent with an added safety risk, unless efficacy data suggest superior benefit compared to other drugs for the same indication, should either not be made available or should be reserved for second line therapy.

Finally, adverse effects such as increases in total cholesterol and large weight gains reported with some of the other antipsychotic agents are unlike sudden death in that they can be identified early and the patient at risk can be switched to another agent. Therefore, the claim that ziprasidone has less cardiovascular risk factors because the drug causes less weight gain and/or improves lipid profile cannot offset its likely

to cause sudden death.

### Introduction

(Please refer to previous consults written by Dr. C. Ganley and dated 12/17/98, 11/18/97, and 2/21/97)

The sponsor of ziprasidone was sent a letter by the Agency on 6-17-98 stating that the drug was not approvable because of its effect on cardiac repolarization. The concern was that the "modest" effect (QTc<sup>1</sup> prolongation of about 10 msec with the 160 mg dose) was an underestimation because the ECGs were not obtained at maximum drug concentration. The study reviewed here was specifically designed to address this issue and also to compare the effect of ziprasidone on cardiac repolarization to the effect of other approved antipsychotic drugs.

### Study Design, protocol #128-054

This was a randomized, open-label, parallel, multi-center study in subjects with normal ECGs (QTc <450 msec) and psychotic disorders. Following a screening phase, the trial consisted of five different treatment periods:

Period 1: subjects who were eligible for enrolling in the study had their current medication tapered over several days as an out-patient;

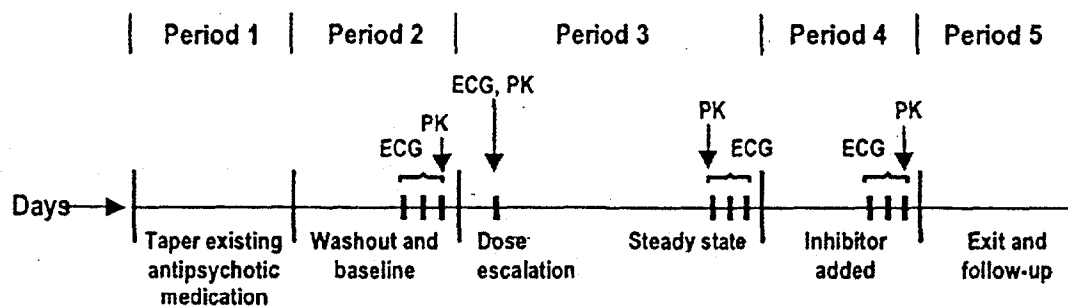
Period 2: subjects entered a clinical research facility to be completely withdrawn from current therapy.

Period 3: subjects were randomized to one of six treatments (ziprasidone, risperidone, olanzapine, quetiapine, thioridazine or haloperidol) with the dose escalated over 10 to 19 days;

Period 4: after the maximum dose of randomized therapy was achieved, the metabolic inhibitor selected for each drug was administered;

Period 5: after steady state is reached with the combination of randomized therapy and a metabolic inhibitor, the subjects were withdrawn from therapy.

The study diagram is shown below.



ECGs were obtained at baseline, at start of study drug (day 2), at steady state (period 3), and with the inhibitor (period 4). ECGs were recorded at times estimated to correspond with the mean T<sub>max</sub> for each study drug.

### Dosing and metabolic inhibitors

Subjects were to be titrated to the highest dose tolerated. The initial and maximum doses used for each

<sup>1</sup> Bazett's correction:  $QTc = QT / \sqrt{60 / \text{hr rate}}$



treatment group and the doses of the metabolic inhibitors are shown below.

Study Drugs (Period 3)	Potency (mg)	Initial Dose (mg/day)	Maximum Dose (mg/day)
Ziprasidone	20, 40, and 80 (capsules)	40	160
Risperidone	1, 2, 3, and 4 (tablets)	2	16
Olanzapine	5 and 10 (tablets)	5	20
Quetiapine	25, 100, and 200 (tablets)	50	750
Thioridazine	25 and 100 (tablets)	50	300
Haloperidol	2, 5, and 10 (tablets)	2	15
<b>Metabolic Inhibitors (Period 4)</b>			
Paroxetine	20 (tablet)	20	
Ketoconazole	200 (tablet)	400	
Fluvoxamine	50 (tablet)	50	100

There were changes with the administration of the inhibitors during period 4:

Originally,

- ketoconazole (200 mg BID) was administered with ziprasidone and quetiapine,
- paroxetine (20 mg QD) was administered with thioridazine and risperidone,
- fluvoxamine (50 mg escalating to 100 mg QD) was administered with olanzapine.
- paroxetine (20 mg QD) and ketoconazole (200 mg BID) were administered with haloperidol.

Late in the study, ketoconazole (200 mg BID) was substituted for paroxetine as the metabolic inhibitor in the risperidone group, and the regimen for dosing ketoconazole to the haloperidol group was changed from 200 mg BID to 400 mg QD by protocol amendment.

Comments on the protocol raised by Dr. Ganley

- 1) the study was to enroll a sufficient number of subjects such that 150 subjects (25 per group) completed the entire study. There was no explanation in the protocol to justify the sample size.
- 2) The protocol was lacking in its description of how the QTc data should be interpreted. There was, however, an expectation that the change in QTc interval with ziprasidone therapy was to be different from haloperidol.

Study results

A total of 183 subjects were randomized and had evaluable ECG data. Patient demographics are shown below.

	Baseline Demographic Characteristics											
	Ziprasidone		Risperidone		Olanzapine		Quetiapine		Thioridazine		Haloperidol	
	Ma	Fb	M	F	M	F	M	F	M	F	M	F
Number of subjects	25	10	22	6	20	8	22	7	25	6	25	7
Mean age (yrs)	38.6	36.1	38.3	37.3	38.2	38.6	38.1	40.6	35.5	37.3	33.7	43.0
Age range (yrs)	22-58	20-47	20-55	29-47	22-58	25-53	26-47	27-57	21-48	30-44	20-47	35-49
Mean weight (kg)	85.9	79.8	84.1	88.0	86.0	86.2	83.9	87.7	90.5	87.1	77.9	75.6

aM=male; bF=female

Mean age and range, mean weight and number of subjects were reasonably similar for the different treatment groups.

There were 8 subjects (2 ziprasidone, 3 quetiapine, and 3 haloperidol who did not reach the protocol-specified maximum daily dose of study drug in Period 3. Seven of the eight were discontinued prematurely. The eighth received 600 mg of quetiapine at steady-state rather than 750 mg because of adverse events. This subject completed the study. One thioridazine subject required a dose higher than that specified in the protocol.

### Heart rate and correction factors

QT interval is inversely related to heart rate (normally, the slower the heart rate the longer the QT interval). To compensate for normal variations in heart rate, the Bazett's correction, known as QTc, is used. The use of Bazett's correction factor is controversial with drugs that increase heart rate. Among the group of drugs studied here, quetiapine was the only one that consistently raised heart rate throughout the study. The mean change from baseline heart rate for the various agents are shown in attachment 1:

### QT/QTc

Baseline is defined as the average of the planned ECGs collected on days -2, -1, and 0. All ECGs were obtained at Tmax and all were read centrally. QTc intervals were provided by the central reader.

### *Mean changes*

The tables below show the mean change QTc and QT from baseline at the start of titration (day 2) and at steady state (period 3).

#### Start of titration

Mean change (SD) from baseline at Day 2: msec

	Zispraside	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QTc	3.0 (10.7)	4.7 (14.1)	0.3 (9.0)	-0.5 (8.6)	11.2 (13.2)	2.2 (12.4)
QT	-3.6 (17.3)	-5.3 (11.2)	-3.7 (12.8)	-0.1 (12.4)	1.1 (16.6)	-0.8 (15.6)

Tables 5.2.2.1 and 5.2.3.2.1

At the start of dosing, only thioridazine shows a substantial prolongation of the QTc (11.2 msec). Changes from baseline in QTc/QT are similar for ziprasidone and the rest of the agents.

#### Steady state

Mean change (SD) from baseline at Period 3: msec

	Zispraside	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QTc	20.6 (16.4)	10.0 (11.1)	6.4 (13.6)	14.5 (12.7)	35.8 (13.5)	4.7 (16.9)
QT	7.0 (18.40)	-11.8 (12.8)	-9.3 (18.0)	-12.2 (15.1)	19.7 (22.3)	12.5 (16.7)

Tables 5.2.2.1 and 5.2.3.2.1

Thioridazine at steady state caused a 35.8 msec increase in QTc (9% increase from baseline) and a 19.7 msec increase in QT (5% increase from baseline). The next largest increase was caused by ziprasidone with a 20.6 msec increase in QTc (5% increase from baseline) and a 7 msec increase in QT (2% increase from baseline). While risperidone, olanzapine, and quetiapine were associated with an increased QTc, the QT was decreased for these agents. Haloperidol increased QTc by 4.7 msec and it is generally accepted, perhaps erroneously, that its effect on QTc is not different from placebo.

With metabolic inhibitor

Mean change (SD) from baseline at Period 4: msec

	Zispradone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Ratio <sup>^</sup>	1.39	2.47	1.77	4.03	1.04	1.94
QTc	20.4 (17.0)	3.2 (16.9)	5.3 (12.8)	19.7 (13.5)	28.0 (17.3)	8.9 (15.0)
QT	9.9 (21.0)	1.1 (18.6)	-1.8 (17.8)	-15.8 (16.9)	33.3 (23.1)	22.5 (19.9)

<sup>^</sup>drug concentrations period 4: period 3

Tables 5.2.2.1, 5.2.3.2.1, and page 38 of study report

Quetiapine showed the largest increase in plasma concentration when subjects were also given a metabolic inhibitor. Compared to steady state, the concentration of ziprasidone increased slightly while the mean QT/QTc prolongation (20.4/9.9 msec) was basically unchanged.

*Outliers*

The tables below shows the number and percent of subjects with QTc increases from baseline of  $\geq 30$ ,  $\geq 60$ , and  $\geq 75$  msec for the various drugs at steady state (period 3) and with the metabolic inhibitor (period 4).

Number and (percent) of subjects Period 3

Increase from baseline	Zispradone N=33	Risperidone 16 mg N=28	Olanzapine N=26	Quetiapine N=27	Thioridazine N=30	Haloperidol N=20
QTc: $\geq 30$ msec	21 (64)	12 (46)	9 (35)	14 (52)	30 (97)	11 (41)
QTc: $\geq 60$ msec	7 (21)	1 (4)	1 (4)	3 (11)	9 (29)	1 (4)
QTc: $\geq 75$ msec	1 (3)	0	0	0	3 (10)	0

Table 5.3.3.2

Number and (percent of subjects) Period 4

Increase from baseline	Zispradone N=32	Risperidone N=20	Olanzapine N=24	Quetiapine N=27	Thioridazine N=30	Haloperidol N=20
QTc: $\geq 30$ msec	25 (78)	8 (40)	8 (33)	8 (67)	27 (90)	9 (45)
QTc: $\geq 60$ msec	4 (13)	0	0	4 (15)	6 (20)	0
QTc: $\geq 75$ msec	1 (3)	0	0	0	4 (13)	0

Table 5.3.4.2

Only thioridazine and ziprasidone increased QTc by 75 msec or more in at least 1 study patient.

*Relationship to drug concentration.*

The attached figures show individual QTc and QT values plotted against drug concentration on a log scale for each of the antipsychotic agents. The steepness of the slope indicates the magnitude of increase in QTc and QT for every log increase in concentration.

Thioridazine and ziprasidone showed the steepest slope for both QTc and QT followed by haloperidol. While the effect of quetiapine on the QTc was impressive (slope of 15), the changes in QT was negative. Olanzapine had a small positive slope and the slope for risperidone was flat.

Lipid profiles

Median changes and median percent changes from baseline at last planned visit prior to discharge in fasting serum cholesterol and triglycerides are shown below by treatment group.

**Serum Lipid Concentrations: Median Baseline (Median Change: mg/dl) and % Change from Baseline**

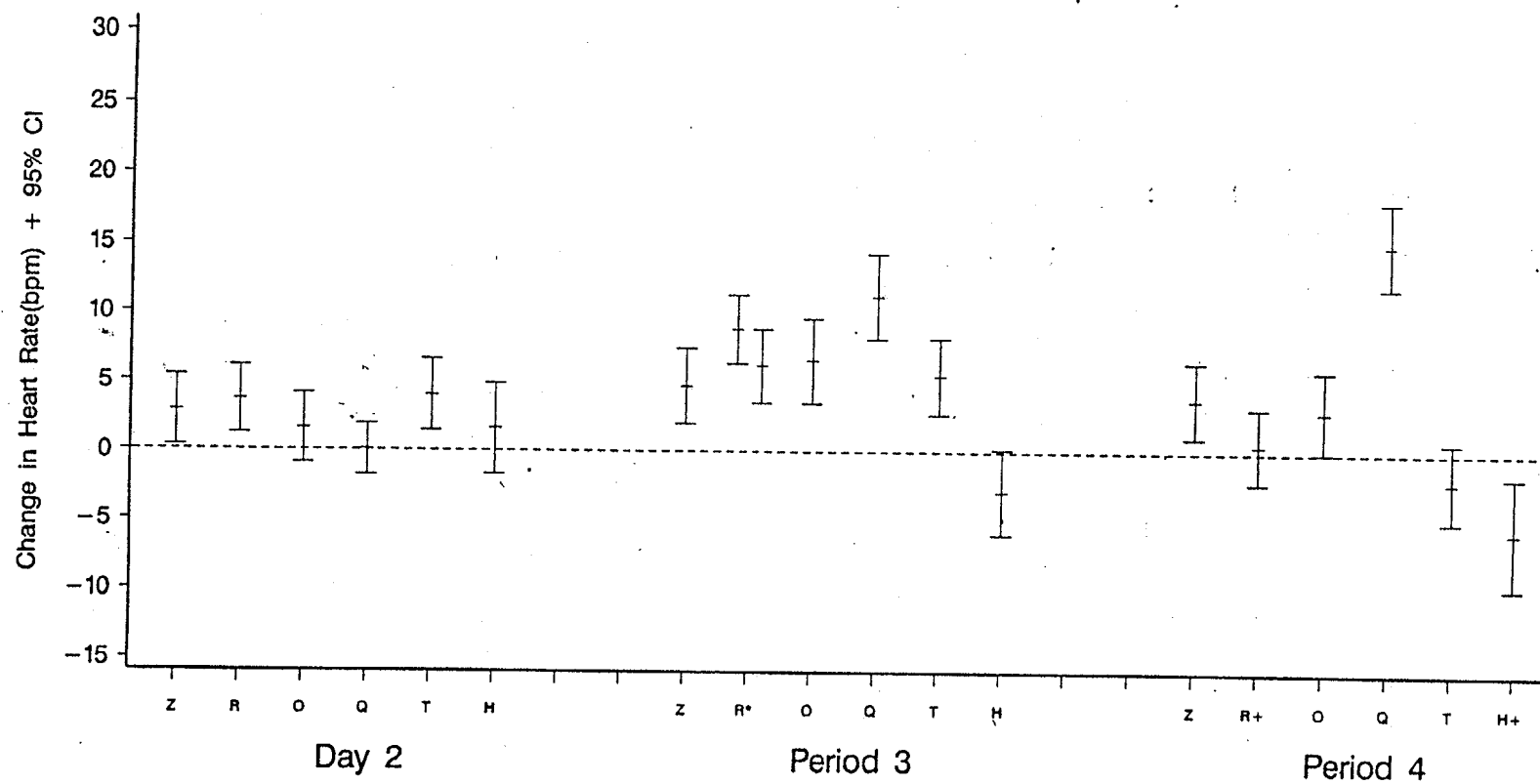
	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Cholesterol						
Total	197.5(-14.5 <sup>c</sup> )	204.0(-3.0 <sup>a</sup> )	201.0(4.0 <sup>f</sup> )	196.0(5.0 <sup>f</sup> )	186.0(21.0 <sup>g,i</sup> )	193.0(-22.0 <sup>c</sup> )
% Change	-7.5 <sup>b</sup>	-1.6 <sup>a</sup>	2.1 <sup>f</sup>	2.4 <sup>f</sup>	13.7 <sup>g,i</sup>	-11.5 <sup>c</sup>
HDL	43.5(0.0)	41.0(-2.0)	44.0(-2.0)	45.0(-3.0)	41.0(1.5)	43.0(-3.0 <sup>b</sup> )
% Change	0.0	-4.9	-4.6	-8.6	3.0	-6.0 <sup>a</sup>
LDL	122.0(-11.0)	125.0(9.0 <sup>a</sup> )	128.0(1.5)	117.0(-0.5 <sup>a</sup> )	121.0(20.0 <sup>g,i</sup> )	121.0(-14.0 <sup>c</sup> )
% Change	-8.5	6.5 <sup>a</sup>	1.1	-0.3 <sup>f</sup>	18.6 <sup>g,i</sup>	-10.5 <sup>c</sup>
Triglycerides	141.0(-37.0 <sup>c</sup> )	158.0(-17.0)	148.0(43.0 <sup>c,i</sup> )	124.0(25.0 <sup>g,i</sup> )	120.0(9.0 <sup>f</sup> )	118.0(-18.0 <sup>b</sup> )
% Change	-28.0 <sup>c</sup>	-6.7 <sup>d</sup>	31.0 <sup>c,i</sup>	18.3 <sup>g,i</sup>	7.9 <sup>f</sup>	-18.0 <sup>b</sup>
Total/HDL Ratio	4.31(-0.33 <sup>b</sup> )	5.43 (0.31 <sup>f</sup> )	5.14(0.28 <sup>f</sup> )	4.42(0.48 <sup>h</sup> )	4.61(0.41 <sup>h</sup> )	4.26(-0.22 <sup>a</sup> )
% Change	-7.5 <sup>b</sup>	5.9 <sup>a*</sup>	5.4 <sup>a*</sup>	10.8 <sup>h*</sup>	12.4 <sup>g,i</sup>	-7.0 <sup>a</sup>

<sup>a</sup>p<0.05; <sup>b</sup>p<0.01; <sup>c</sup>p<0.001 versus baseline using Wilcoxon signed rank test on change from baseline values against 0; <sup>d</sup>p<0.05, <sup>e</sup>p<0.01, <sup>f</sup>p<0.001 versus ziprasidone by two-sided Wilcoxon test.

The sponsor claims that ziprasidone has a beneficial effect on lipid profiles. In the Division's opinion, if patients need control of their lipids, treating them with a lipid lowering agent would be preferred.

Figure 2.2

Mean Change from Baseline Heart Rate(bpm) and 95% Confidence Intervals at Each Period by Treatment Group – All Subjects  
Ziprasidone Protocol 054



Z=Ziprasidone, R=Risperidone, O=Olanzapine, Q=Quetiapine, T=Thioridazine, H=Haloperidol.

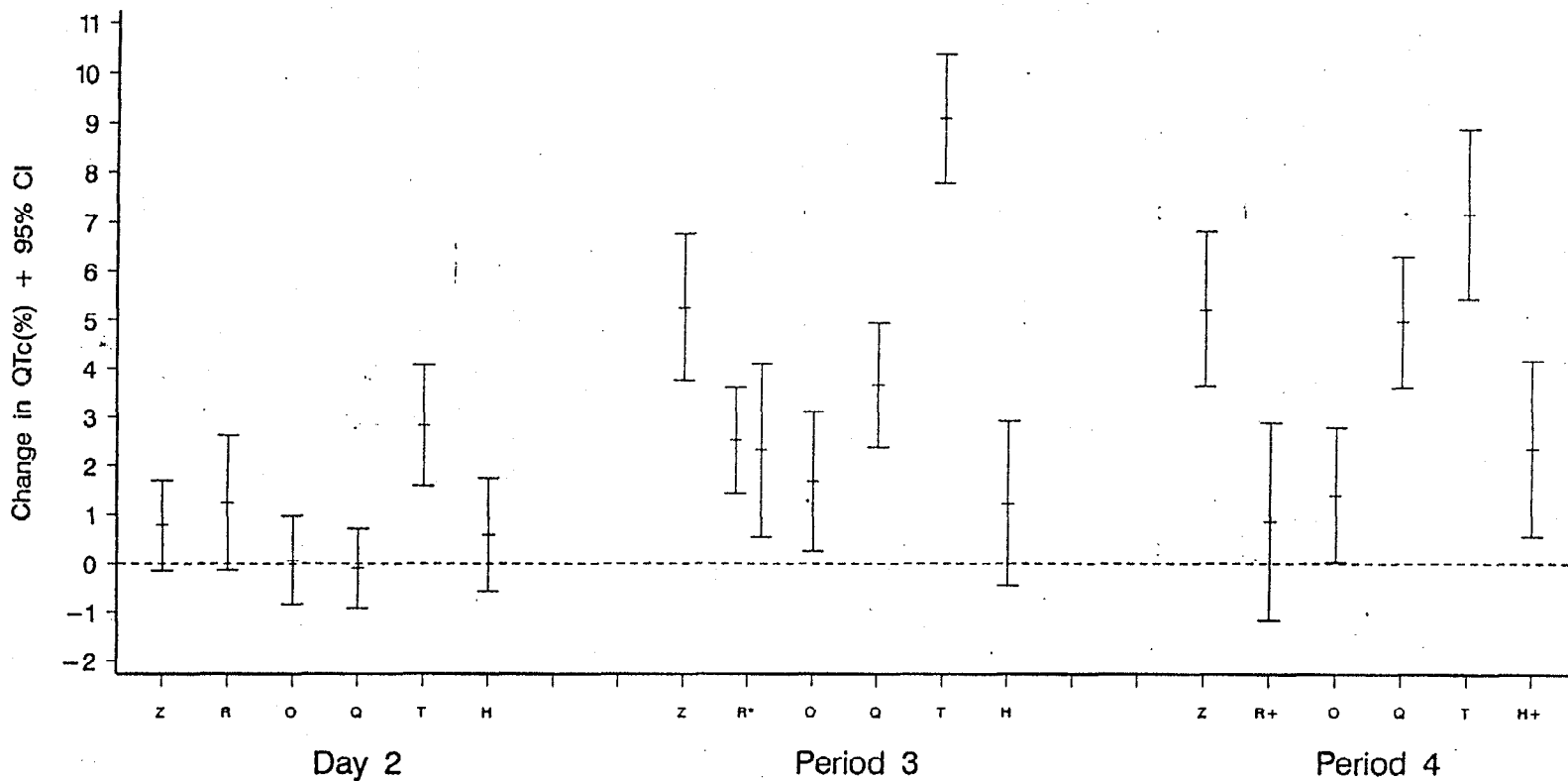
\* Bar on left is Risperidone 6-8 mg, bar on right is Risperidone 16 mg.

+ Contains only pre (3/16/99) amendment values, post-amendment values are provided in the listings.

Source Data: Table 5.2.2.2.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Figure 1.2.2

Percent Change from Baseline QTc Interval(msec) and 95% Confidence Intervals at Each Period by Treatment Group – All Subjects  
Ziprasidone Protocol 054



Z=Ziprasidone, R=Risperidone, O=Olanzapine, Q=Quetiapine, T=Thioridazine, H=Haloperidol.

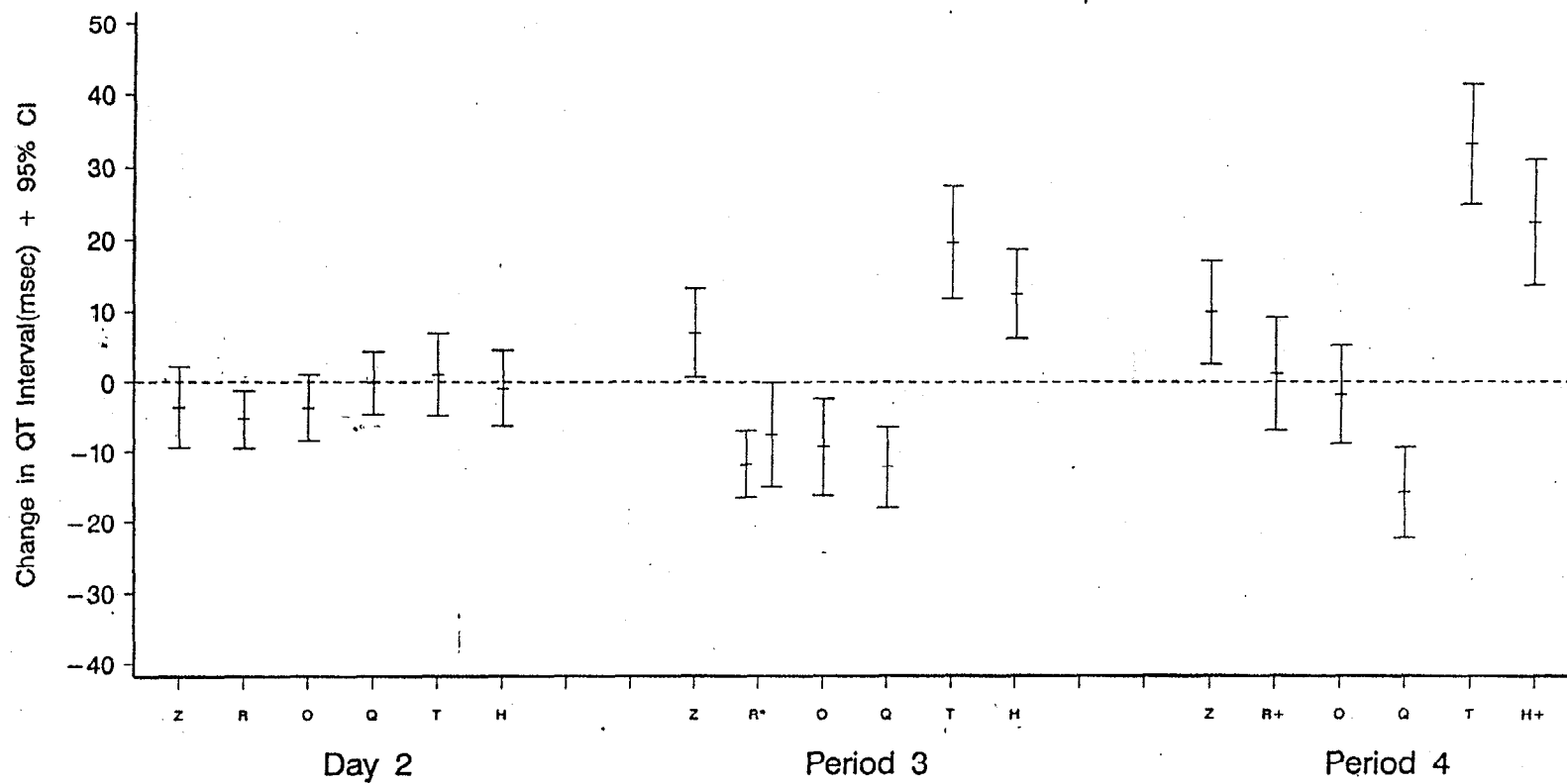
\* Bar on left is Risperidone 6-8 mg, bar on right is Risperidone 16 mg.

+ Contains only pre (3/16/99) amendment values, post-amendment values are provided in the listings.

Source Data: Table 5.2.1.2.2. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Figure 3.2

Mean Change from Baseline QT Interval(msec) and 95% Confidence Intervals at Each Period by Treatment Group – All Subjects  
Ziprasidone Protocol 054



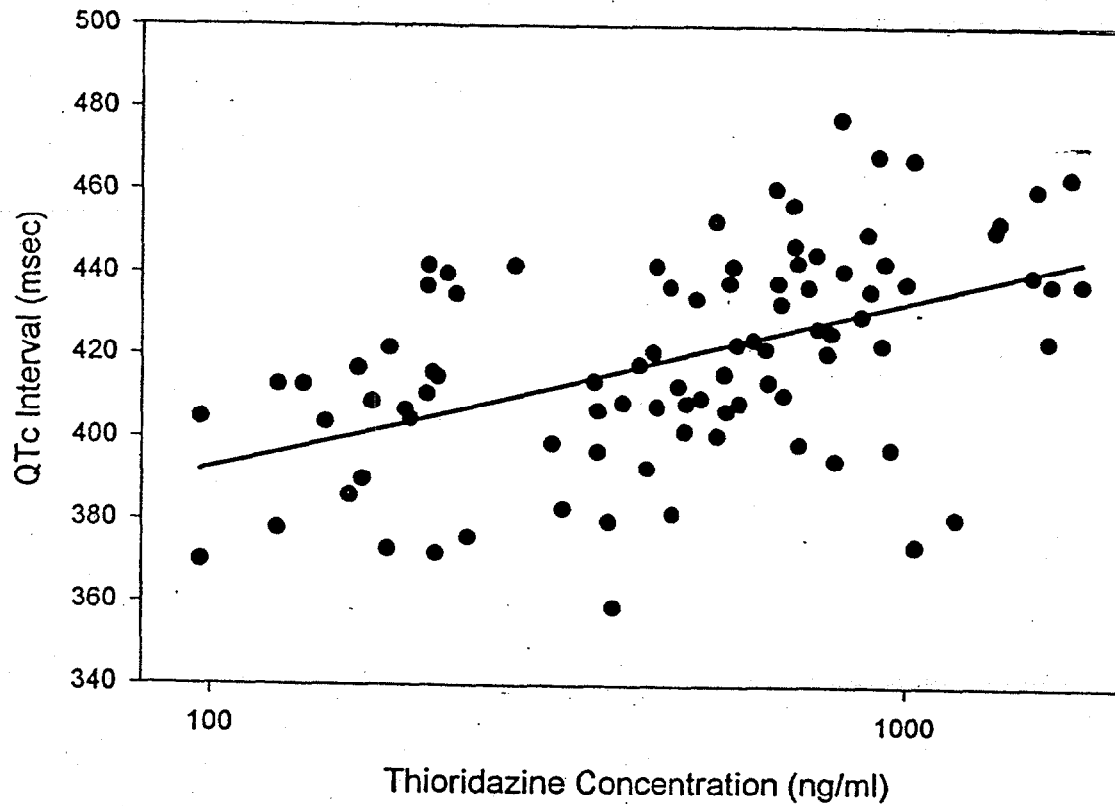
Z=Ziprasidone, R=Risperidone, O=Olanzapine, Q=Quetiapine, T=Thioridazine, H=Haloperidol.

\* Bar on left is Risperidone 6-8 mg, bar on right is Risperidone 16 mg.

+ Contains only pre (3/16/99) amendment values, post-amendment values are provided in the listings.

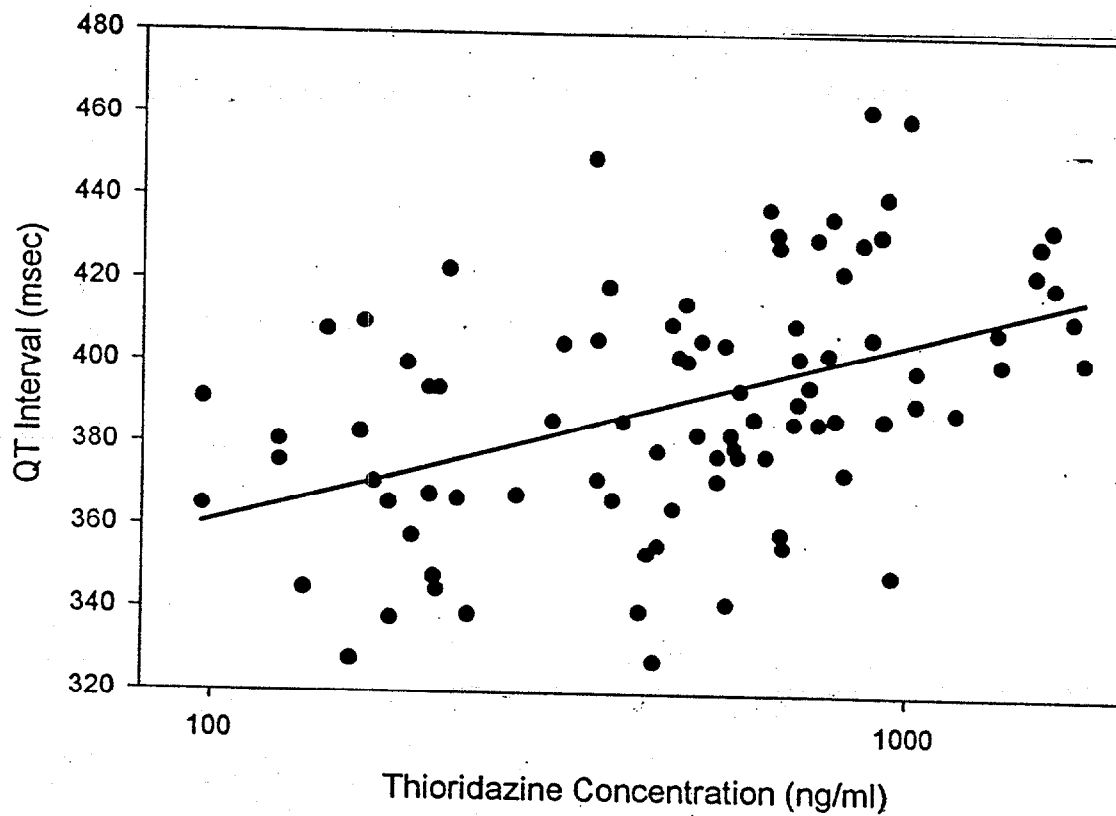
Source Data: Table 5.2.3.2.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

### Effect of Thioridazine on QTc Interval



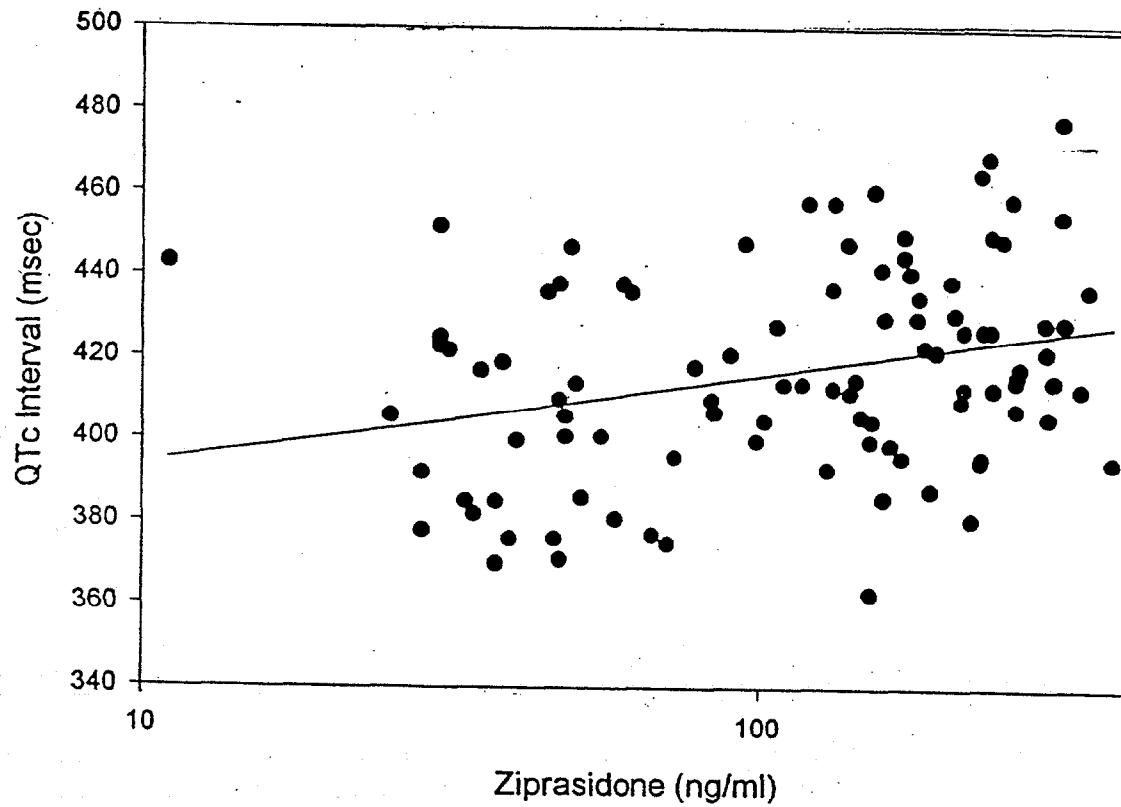


### Effect of Thioridazine on QT Interval



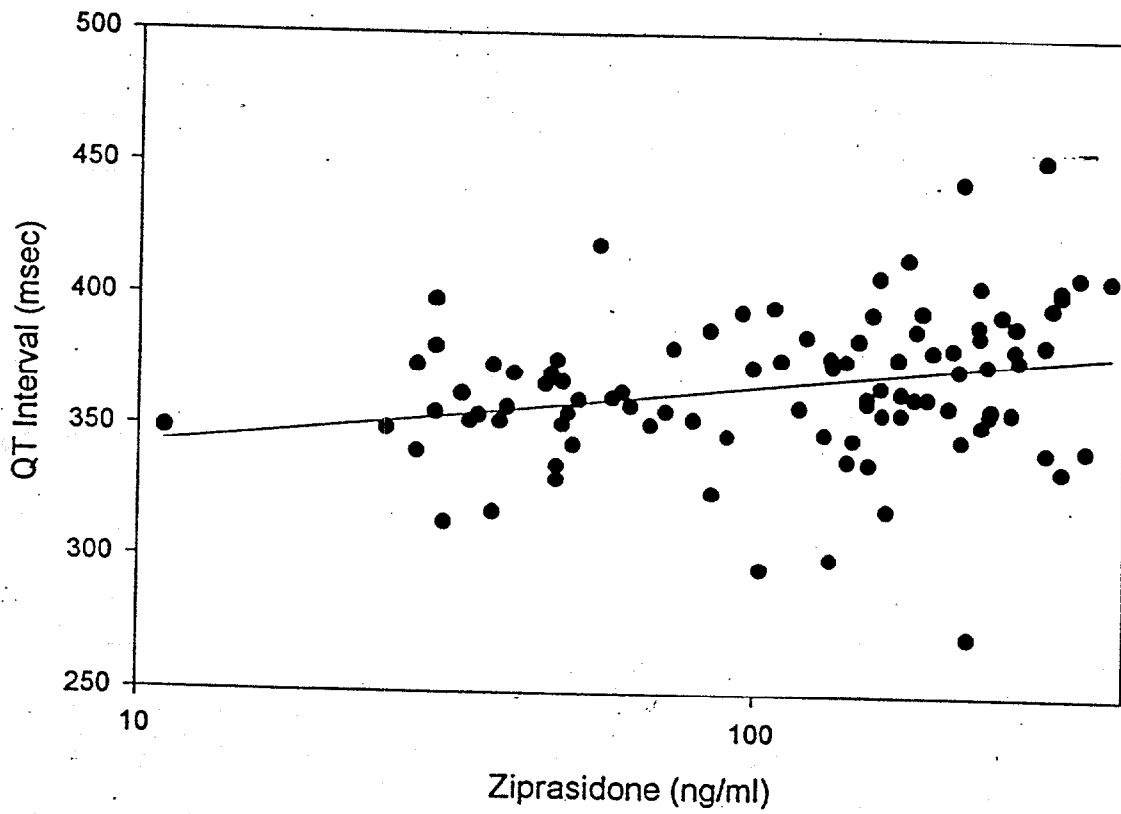
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Slope = 44.17474  
 $r^2 = 0.2164634033$

### Effect of Ziprasidone on QTc Interval



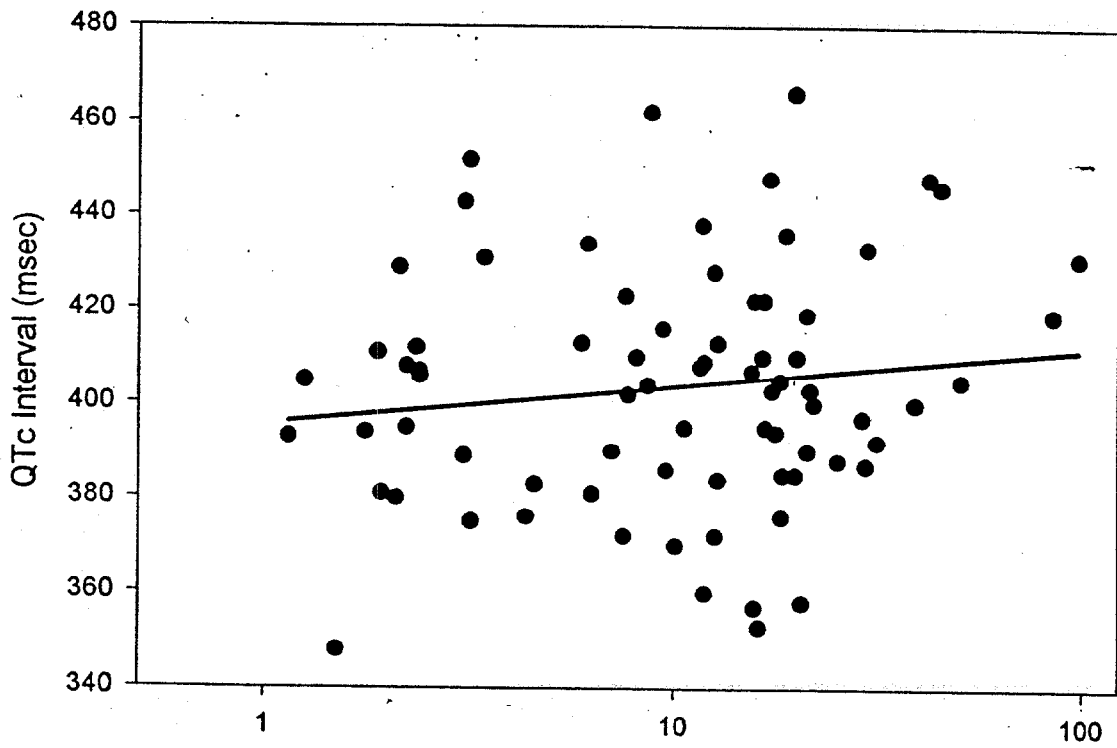
Intercept = 372.711  
Slope = 21.57282  
r<sup>2</sup> = 0.09080

### Effect of Ziprasidone on QT Interval



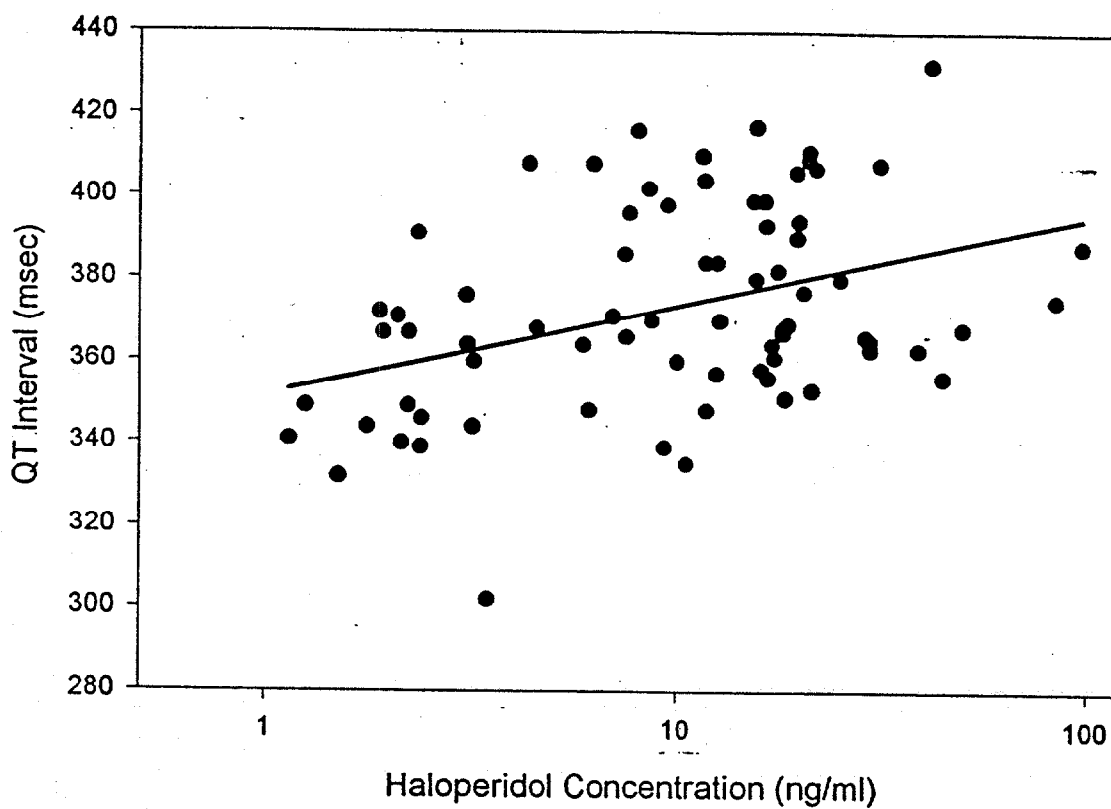
Intercept = 319.724  
Slope = 23.342  
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### Effect of Haloperidol on QTc Interval



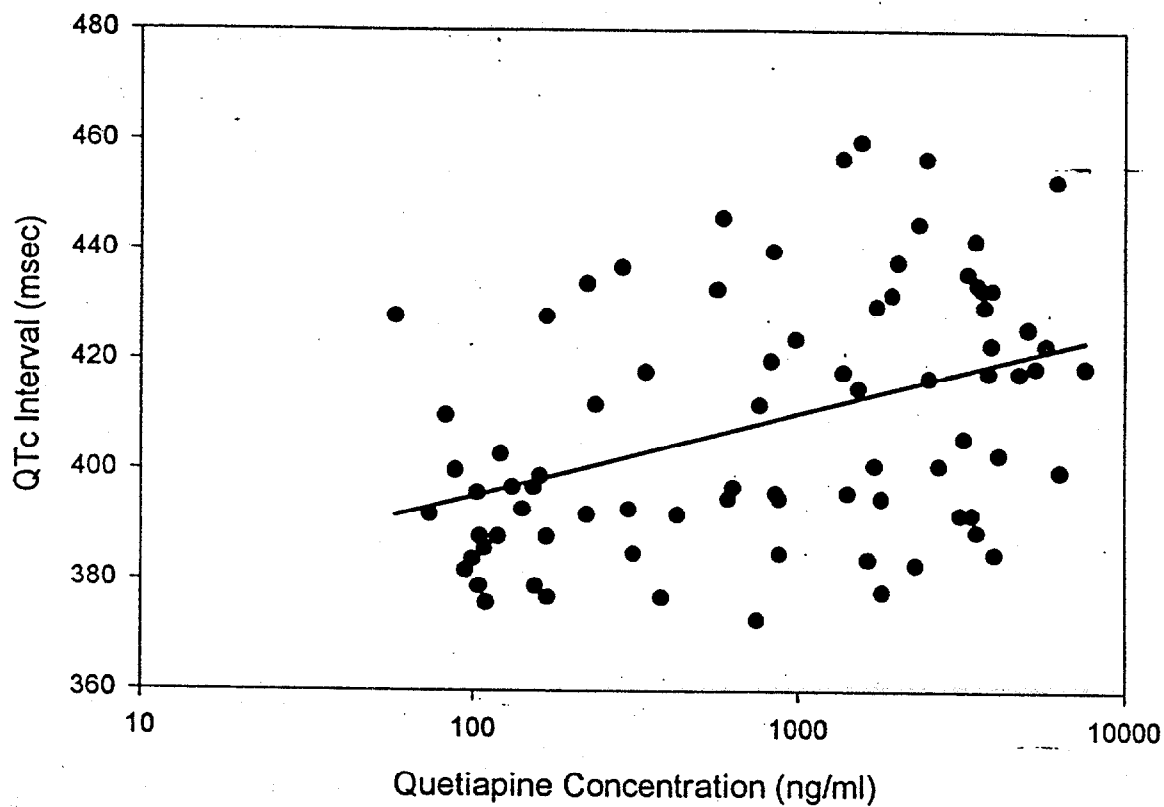
Intercept = 395.6947  
Slope = 8.0848  
 $r^2=0.02004478$

### Effect of Haloperidol on QT Interval



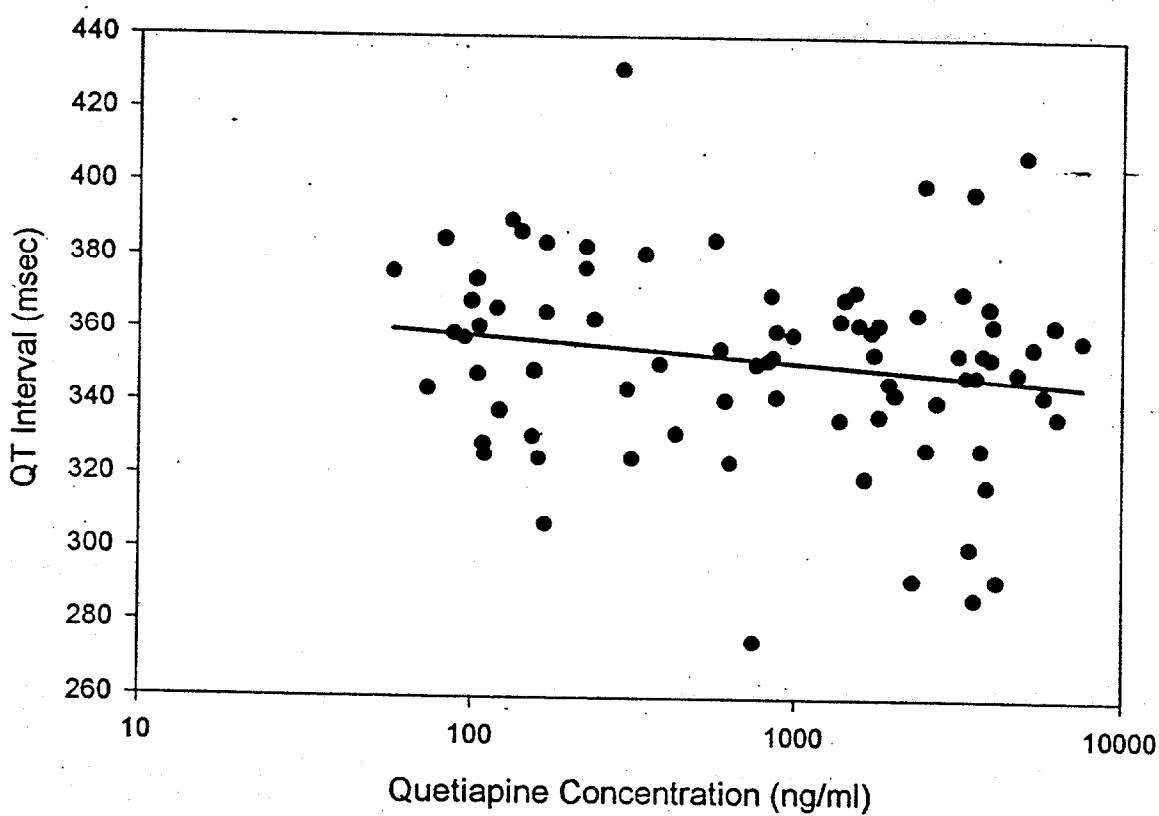
Intercept = 351.81535  
Slope = 21.5923  
 $r^2=0.1552740511$

### Effect of Quetiapine on QTc Interval



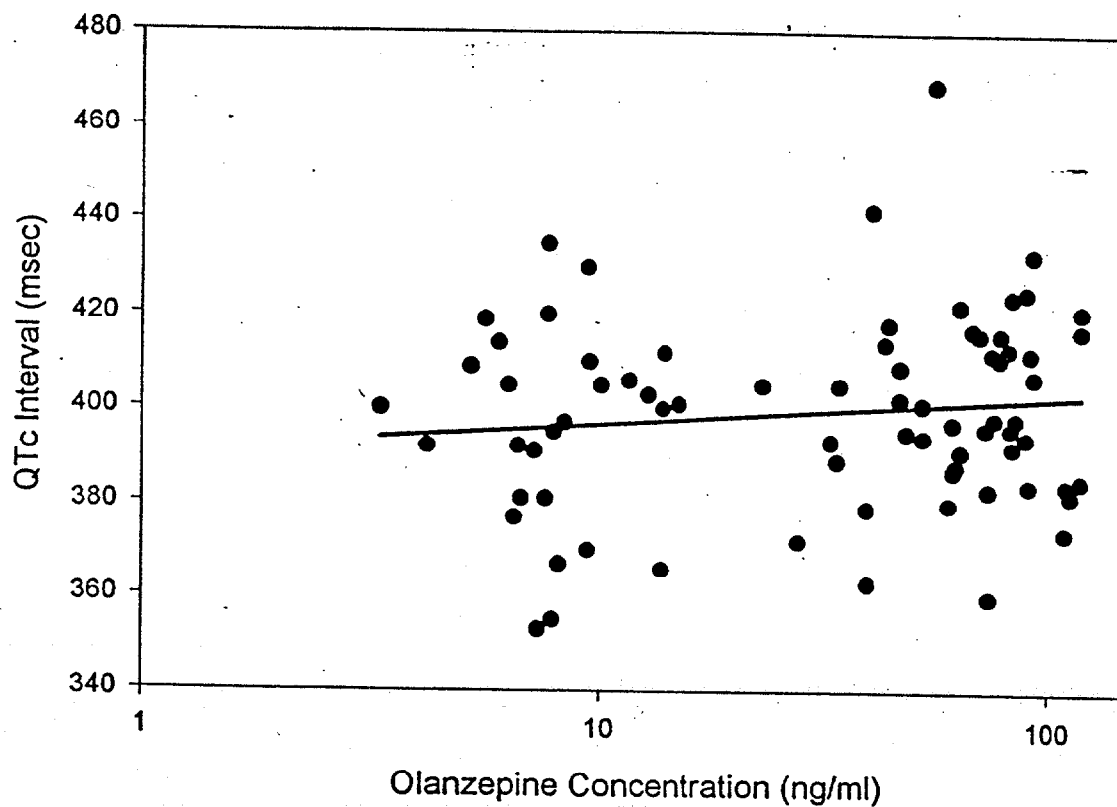
Intercept = 365.1656  
Slope = 15.0783  
 $r^2 = 0.1713726855$

### Effect of Quetiapine on QT Interval



Intercept = 372.6992  
Slope = -7.116431  
 $r^2 = 0.0269297523$

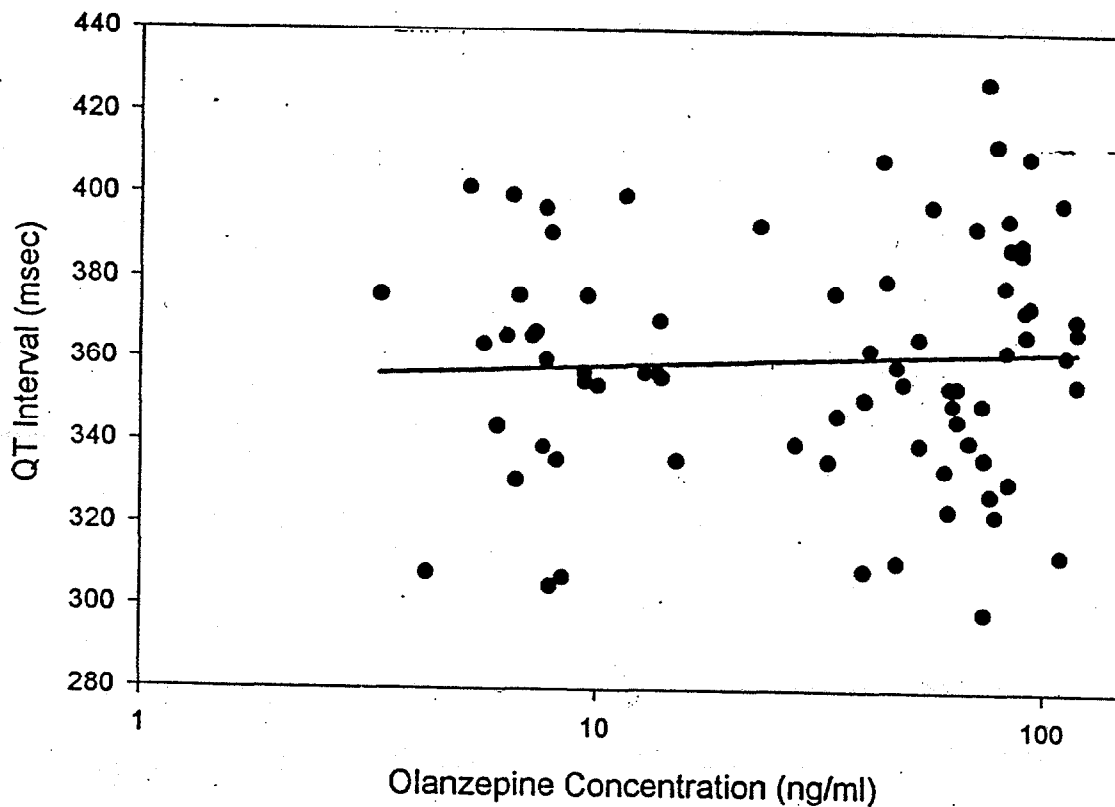
### Effect of Olanzapine on QTc Interval



Intercept = 390.7492  
Slope = 5.81969  
 $r^2 = 0.0177752817$

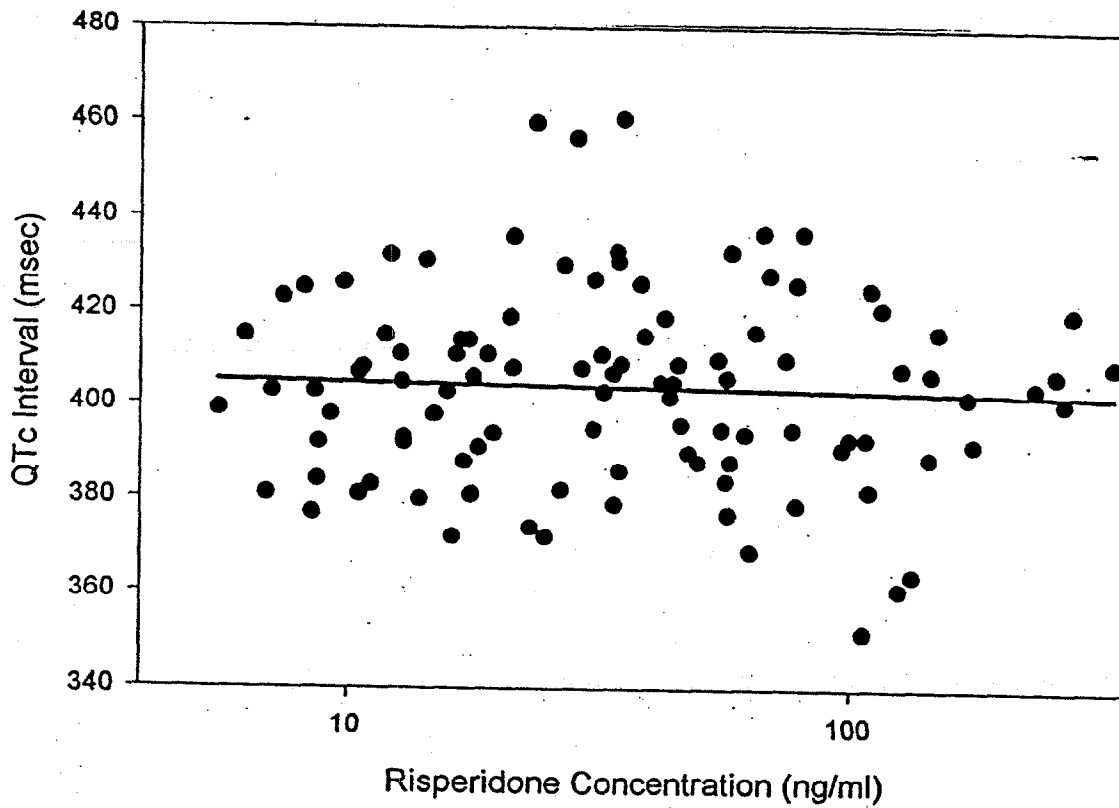


### Effect of Olanzapine on QT Interval

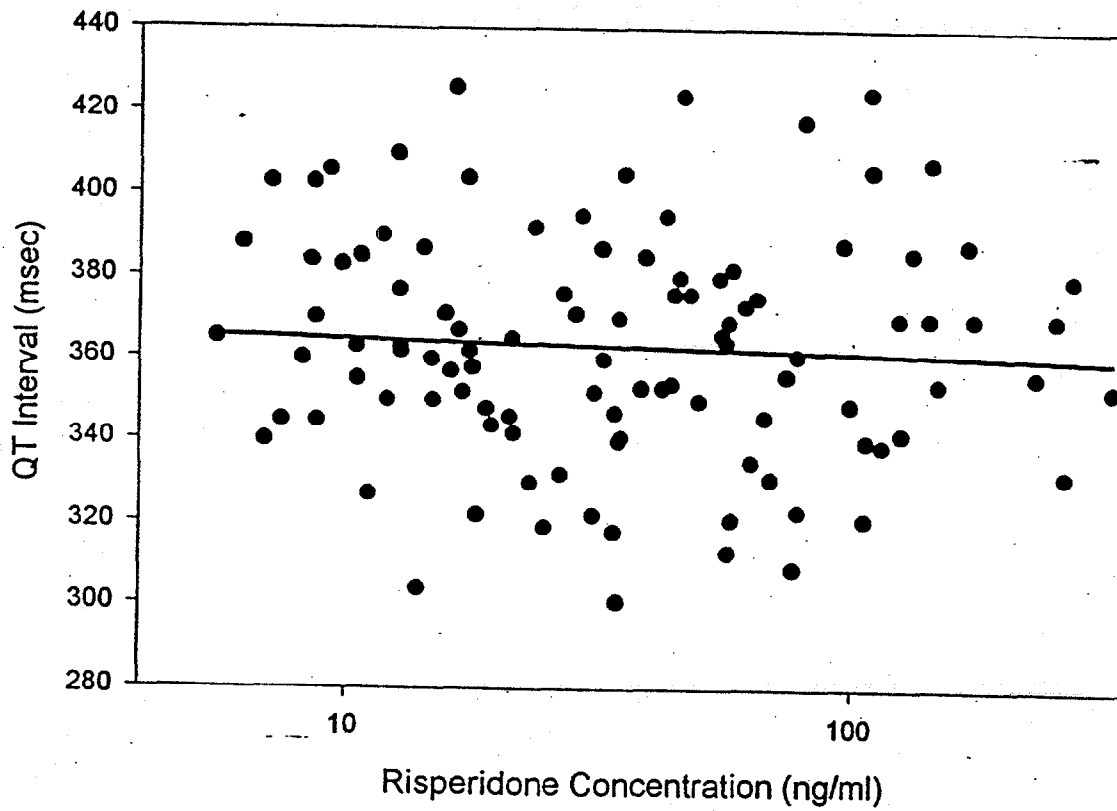


Intercept = 354.47023  
Slope = 3.9619  
 $r^2 = 4.262398787e-3$

### Effect of Risperidone on QTc Interval



### Effect of Risperidone on QT Interval



Intercept = 367.81725  
Slope = -3.157232  
 $r^2 = 2.4245779374e-3$