Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death

1. **Describe the case or problem that attracted you to this paper**
A 57 yo man known to have schizophrenia being treated with Thioridazine (Mellaril) was admitted with atypical chest pain to the cardiology service. His EKG didn’t show any ischemic change, however, he was found to have prolonged QT (QTc 470 msec). His serial trop and stress test was negative. His Mellaril was changed to Olanzapine (Zyprexa) and he was discharged home. No followup EKG was done.

2. **Explain how you came across this article**
Paper found by searching pubmed clinical under the heading “atypical antipsychotics and sudden cardiac death”

3A. **Describe the study**
It is a retrospective cohort study of Medicaid enrollees in Tennessee. The adjusted incidence of sudden cardiac death among current users of antipsychotic drugs was calculated.

3B. **Describe the research question**
Over a period from Jan 1, 1990 till Dec 31, 2005, all persons enrolled in Medicaid got screened. The users were either on typical or atypical antipsychotics. The cohort also included two controls for each user of antipsychotic drugs. The risk of sudden cardiac death associated with the use of the two classes of antipsychotic drugs was calculated.

4. **State the importance/relevance/context of the question**
Typical antipsychotic drugs are known to increase risk of sudden cardiac death by prolonging the QT interval. Less is known about the cardiac safety of the atypical antipsychotic drugs, which have largely replaced the older agents in clinical practice. Several atypical antipsychotic drugs prolong ventricular repolarization. Although torsades de pointes has been reported in persons using atypical antipsychotic drugs, whether these drugs increase the risk of sudden cardiac death to the same extent as the older medications is unknown.

5. **Describe the methods by giving more detail on the components of the question**
The study included 44,218 and 46,089 users of single typical and atypical drugs, retrospectively, and 186,600 matched nonusers of antipsychotic drugs. The cohort was restricted to persons 30 to 74 years of age. The end point excluded
deaths of patients who had been admitted to the hospital, deaths that were not sudden, and deaths for which there was evidence of an extrinsic.

6. **State your answers to the Critical appraisal questions on validity**

Users and nonusers of antipsychotic drugs had similar baseline demographic characteristics. The cohort included two controls for each user of antipsychotic drugs, matched for age, sex, and first day of follow-up, who were randomly selected from qualifying nonusers of antipsychotic drugs on the first day of follow-up.

Follow-up extended from the first qualifying day until the end of the study period, the death of the person, the termination of Medicaid enrollment, or the date on which eligibility criteria for inclusion in the cohort were no longer met.

7. **Summarize the primary results**

Current users of typical antipsychotic drugs had an adjusted rate of sudden cardiac death that was twice that for nonusers (incidence-rate ratio, 1.99; 95% confidence interval [CI], 1.68 to 2.34). A similar increased risk was seen for current users of atypical antipsychotic drugs, who had a rate of sudden cardiac death that was more than twice that for nonusers (incidence-rate ratio, 2.26; 95% CI, 1.88 to 2.72) and that did not differ significantly from the rate for users of the typical agents (incidence-rate ratio for users of atypical as compared with users of typical antipsychotic drugs, 1.14; 95% CI, 0.93 to 1.39).

The risk of sudden cardiac death increased with an increasing dose among current users of typical or atypical antipsychotic drugs (Fig. 1). Among users of the typical agents, the incidence-rate ratios increased from 1.31 (95% CI, 0.97 to 1.77) for persons taking low doses to 2.42 (95% CI, 1.91 to 3.06) for those taking high doses (P<0.001 for dose–response relationship). Among users of the atypical drugs, the incidence-rate ratios increased from 1.59 (95% CI, 1.03 to 2.46) for persons taking low doses to 2.86 (95% CI, 2.25 to 3.65) for those taking high doses (P = 0.01 for dose–response relationship).

8. **Describe why you think the results can or cannot be applied to your patient/situation**

Our patient falls in the age category of the group of the study. He doesn’t have any cardiovascular risk factors which would put him at higher risk. The prolonged QTc was thought to be secondary to the typical antipsychotics. No repeat EKG was done after the switch to the atypical antipsychotic to followup on the
prolonged QTc. It seems that switching him to atypical antipsychotic wouldn’t decrease his risk of SCD.

9. Conclude with your own decision about the utility of the study in your practice - Resolve the case or question with which you began

Atypical antipsychotics have similar risk for sudden cardiac death as typical antipsychotics. They should be avoided or used with caution in patients at high risk for cardiac arrhythmia. The lowest possible dose should be used, as the risk of SCD is dose dependent.