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Sudden Death in Psychiatric Patients Is Multifactorial

To the Editor: With interest, we read the article by Manu et al¹ about a retrospective study on the causes of and risk factors for sudden death in a cohort of psychiatric patients dying suddenly (< 1 h witnessed, <24 h unwitnessed) during a period of 26 years in a single US center. The authors identified 100 patients experiencing sudden death over the observational period, among whom the cause was identified in 48 cases. In 52 patients, the causes of sudden death remained unexplained. We have the following comments and concerns.

The main shortcoming of the study is its retrospective design. Since patients experiencing sudden death were not investigated postmortem according to a mandatory protocol, some causes of sudden death may have been missed. Furthermore, it is unclear if all 100 included patients had undergone autopsy, genetic tests, and toxicologic investigations.

Surprisingly, the prevalence of sudden death continuously increased over 26 years. Was this finding due to increasing awareness of the condition or due to change in definition of sudden death? Was the same definition applied during all 26 years?

A further shortcoming of the study is that a number of risk factors for sudden death were not considered. These include smoking, hereditary cardiac or neurologic disease, Takotsubo syndrome, noncompaction, pulmonary disease (including neurogenic pulmonary edema), and non-antipsychotic drugs.

Interestingly, no embolic strokes were identified as cause of sudden death, although it is conceivable that some of the 100 patients had atrial fibrillation, severe heart failure, dilated cardiomyopathy, noncompaction, patent foramen ovale, or Takotsubo syndrome, which are all conditions associated with intraventricular thrombus formation and thus represent a high risk for cardioembolic stroke. We should know if there was truly no embolic stroke responsible for sudden death and if these common causes were ruled out as possible causes of sudden death.

Missing is an extensive family history to determine if there were any indications for hereditary disease associated with an increased risk for sudden death, such as hereditary ventricular arrhythmias, cardiomyopathy, noncompaction, or genetic epilepsy. How many of the 100 patients had undergone echocardiography and electrocardiography prior to sudden death, and which abnormalities were found? Previous electrocardiographic, echocardiographic, and cerebral magnetic resonance imaging (MRI) findings would be particularly interesting for the 52 patients with unknown cause of sudden death.

In 2 patients, sudden death attributed to myocarditis.¹ We should know if myocarditis was diagnosed by endomyocardial biopsy or by cardiac MRI. Which of the findings were via cardiac MRI, and which were via biopsy?

Brain hemorrhage is nonspecific. We should know if the authors mean intracerebral mass bleeding or subarachnoid bleeding. It should be indicated if bleeding was diagnosed on autopsy or according to postmortem imaging.

We also should know why the inclusion of patients was restricted to those under 74 years of age. Patients aged 74 years or older may die suddenly as well.

Overall, this interesting study has a number of shortcomings, which should be addressed before final conclusions are drawn. The spectrum for causes of sudden death is much broader than considered in this retrospective review. Missing are an extensive family history, genetic tests, and consideration of a number of acquired diseases that may be responsible for sudden death.

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Dr Manu Replies

To the Editor: Dr Finsterer and colleagues question data, derived from a retrospective cohort study my colleagues and I published 10 years ago,¹ regarding sudden deaths among patients receiving care in a psychiatric institution that found that a plurality of deaths were due to cardiovascular causes, primarily coronary artery disease. They think that we had no mandatory protocol for establishing the cause of death and that we did not present information regarding “a number of risk factors” for sudden death. They seem to be particularly concerned about the absence of embolic stroke among the causes of sudden death identified in our 100-case cohort, because they felt that “it is conceivable that that some of the 100 patients had atrial fibrillation, severe heart failure, dilated cardiomyopathy, noncompaction, patent foramen ovale, or Takotsubo syndrome.” They also wondered how many of the patients included in the cohort had electrocardiograms prior to sudden death.

Before addressing the specific comments, I need to present the background of our work, which was the publication, in 2009, in the *New England Journal of Medicine*, of a retrospective cohort study² that indicated a significantly higher risk of sudden cardiac death among persons who had been prescribed antipsychotic drugs. This highly influential study was based of death certificates and was conducted by epidemiologists, and it concluded that the excess of sudden dying may have been due to the known effect of antipsychotic drugs on myocardial repolarization leading to lethal ventricular arrhythmia. Our data indicated that unexplained sudden deaths in psychiatric patients were not associated with higher utilization of first- or second-generation antipsychotics.

Contrary to to the impression of Dr Finsterer and colleagues, our study was based on a structured protocol of multidisciplinary root cause analysis with access to all relevant information and expert opinions. The process was described in detail in our work. We also made clear in our publication that in each case all available electrocardiograms, which were recorded for all according to our hospital's policy, were carefully reviewed to determine the corrected QT interval and all other significant abnormalities.

We had no reason to doubt the fact that work using structured root cause analyses was clearly superior to that based on death certificates. However, in this cohort, only 18 of the 100 patients were accepted by the Medical Examiner of the City of New York for autopsy and the report made available to the root cause analysis team. In a study published a few years later,³ we evaluated data derived from another cohort of patients, all diagnosed with schizophrenia, who died suddenly while admitted for psychiatric care. For that cohort, autopsy data were available in 51 of 57 cases and indicated that in a majority of cases the cause of death was myocardial infarction.

The absence of embolic strokes among the causes of death identified by us is related to the rarity of this association. In the only large study available,⁴ among 255 deaths caused by a first stroke, 52 were sudden, but only 2 were due to cortical or pontine infarction. All other stroke-related sudden deaths were associated with primary intracerebral or subarachnoid hemorrhages.

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