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A Rational Approach to Risk Management of Suicidality vs. Torsades de Pointes (TdP) in Relation to the Prescribing of Antipsychotic Medication

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Abstract

Risk-benefit analysis and management is a core responsibility of physicians during the process of formulating and implementing a comprehensive and effective treatment plan. This assumes particular importance when working with individuals diagnosed with schizophrenia who are confronted with a 5% lifetime risk of completed suicide, as well as the risk of Torsades de Pointes (TdP), a lethal tachydysrhytmia, as a result of antipsychotic medication management. However, the actual risk of such an event, based upon recent epidemiologic data, is less than one-sixth that of completed suicide. Consequently, due consideration must be given to these data while constructing the medication component of a biopsychosocial treatment plan, as avoidance or under-prescribing of antipsychotics places an individual with schizophrenia at greater risk of completed suicide than that of TdP.

Keywords: Schizophrenia, Suicide risk, Torsades de Pointes, Antipsychotic medication management.

Abbreviations: TdP-Torsades de Pointes, SCD-Sudden Cardiac Death, AWP-Average Wholesale Price.

Risk-benefit analysis is a core professional responsibility of physicians. It assumes particular importance when prescribing drugs such as antipsychotics with a potentially lethal side effect, namely Sudden Cardiac Death (SCD) from Torsades de Pointes (TdP). However, it is also an imperative to place this risk in perspective when treating patients at high risk of suicide to minimize the under-prescribing of antipsychotics, as part of a comprehensive treatment plan.

Antipsychotic pharmacotherapy is a cornerstone in the management of schizophrenia, a serious and persistent mental illness with devastating effects on social-occupational functioning. Such treatment is of particular importance early in the course of illness, since relapse prevention at this juncture augurs for improved outcomes. Completed suicide, however, is an outcome and is the most devastating of schizophrenic illness, with an approximate lifetime risk of 5%. Given an expected adulthood of fifty years, this correlates with an annual risk of 1/1000 or a daily risk of 3 completed suicidal events per 1 million patient-days over the average lifespan of an individual with Schizophrenia. Furthermore, it remains to be determined if this rate has increased given the recent CDC report of a general population elevation in completed suicide of greater than 25% since 1999 [1-3].

However, the aforementioned discussion is in no way intended to overlook other significant (and more common) Side effects of antipsychotic medication, including extrapyramidal movement disorders and metabolic syndrome. These factors must also be taken into consideration during any risk-benefit analysis/treatment planning session. For example, individuals with a history of tardive dyskinesia would be exposed to less risk if prescribed a second generation antipsychotic instead of a first generation one. In addition, obese individuals, and those with DM type II, would be better served with a prescription for a first generation antipsychotic [4].

It is important to note that the risk for completed suicide is not uniformly distributed throughout life, with a greater frequency of occurrence early in the course of the illness. It is also important to note that suicidal behavior (i.e., suicide attempt) is at least ten times more likely to occur throughout life in both schizophrenia and other psychiatric conditions. In total, per day risk of combined suicide attempts and completion is much higher than 3 occurrences per 1 million patient-days [5-7].

The QT interval corrected for heart rate (QTc) on the ECG is the current standard used to assess risk to help determine whether to prescribe a medication purported to be associated with TdP, such as an antipsychotic. However, use of this measure is neither a sensitive nor specific risk predicting indicator for a given individual. An additional challenge is a lack of consensus with respect to the use of QT correction formulas, QT nomograms, and what specifically defines QTc prolongation when using surface ECGs in this manner [8,9].

Databases used to assess TdP risk rely on voluntary reports that may not account for confounders (e.g., electrolyte abnormalities) and are prone to over-reporting for certain culprit drugs that are prescribed in high volume (e.g., Quetiapine). Furthermore, these databases do not assess risk based on incidence (TdP cases per time interval of exposure to the culprit drug). Rather, they compare the frequency of TdP reports and/or QTc prolongation without TdP from a culprit drug to all drugs in the same or other therapeutic classes. Other large centralized databases compare the risk of TdP and/or QTc prolongation from culprit drugs in a class to the total of all drug side effects in the same or other drug classes. None of these approaches accurately reflects the rate of actual TdP occurrences in a time period of exposure to one culprit drug (the true definition of incident risk in the field of epidemiology) [10].

Recently, to more accurately assess TdP risk, we combined a strict numerator definition for TdP immediately proceeded by a QTc interval of at least 450 ms with exclusions of confounders for the numerator, and derived the denominator from available annual revenue data for the same culprit drug. The methodology used required estimation of annual drug exposure. The 12-month period closest to the year that encompassed most of the literature reports of TdP cases was used to estimate patient exposure. For drugs without reports of TdP, the 12-month period just before the loss of U.S. market exclusivity was used. These time periods were inclusive of literature reports involving overdoses of the culprit drug that did not result in TdP events.

Very rough estimations of annual worldwide revenues reported by the pharmaceutical manufacturer holding U.S. patent protection for the culprit drug through a variety of open sources were accessed. This dollar figure was then divided by the Average Wholesale Price (AWP) per day for the most commonly used total oral daily dose of the culprit drug. The dividend was then multiplied by an estimate of the number of days per year that a patient would be expected to ingest the culprit drug. The assumptions used for this number was 365 days per year for antipsychotics, 10 days per year for Fluoroquinolones, and based on an annual prevalence of seasonal allergic rhinitis, perennial rhinitis, and mixed rhinitis, 138 days per year for antihistamines. The calculations are summarized as follows: $ Revenues=$AWP=day days=year exposed ¼ annual patient-days

Using these criteria, we found (to a sensitivity of 1:100,000,000) that TdP risk from antipsychotic drugs ranges between a high of 44 TdP events per 100,000,000 exposures in patient-days for Thioridazine to a low of 0.00874 TdP events from Olanzapine ($P<0.0001$). Indeed, the TdP risk from olanzapine and Aripiprazole was similar to the risk for over the counter non-sedating antihistamines (Fexofenadine, Cetirizine, and Loratadine). Ziprasidone and Quetiapine had TdP risks similar to those of levofloxacin and ciprofloxacin, with haloperidol and risperidone demonstrating a TdP risk similar to Astemizole's (a non- sedating antihistamine removed from the US market due to TdP) [11].

It is essential to consider the relative importance of risk factors in clinical decision-making during treatment of individuals with conditions associated with psychosis, especially Schizophrenia. The lifetime risk of completed suicide in patients with Schizophrenia of 3 per 1 million patient-days is considerably greater than that of even the highest risk TdP drug (Thioridazine-0.44 per 1 million patient-days) according to our data, producing a Relative Risk (RR) of 6.8 [3,11].

In fact, certain clinical factors conspire to further heighten this risk such as positive psychotic symptoms, anxiety/agitation, and insomnia in a setting of acute symptom onset [4]. Appropriately aggressive antipsychotic medication management is essential in such a clinical context. Indeed, even in a subacute setting, any one or a combination of the aforementioned symptoms is worrisome, further increasing suicide risk. Given these considerations, it is fairly clear that under prescribing or avoidance of antipsychotic medication for individuals with schizophrenia places them at a much greater risk for suicidal behavior than for TdP. A similar decision making process occurs with respect to the under prescribing of Clozapine, the most effective atypical antipsychotic for treatment resistant Schizophrenia [12,13].

Although multiple factors contribute to Clozapine's underutilization, concern over the risk of Agranulocytosis is significant even though its lifetime risk of less than 1% is one-fifth that of completed suicide [14,15].

In conclusion, TdP is an extremely rare, but lethal, ventricular Tachydysrhythmia that is associated with the use of antipsychotic medications. This is an important consideration when formulating the medication component of a treatment plan for an individual with Schizophrenia, especially in clinical situations in which confounding factors (e.g., electrolyte abnormalities) are minimal or non-existent. However, the substantial and greater risk of suicidal behavior must be given serious consideration for a truly comprehensive and patient focused plan, which also includes consideration of less acutely serious outcomes (e.g., tardive dyskinesia, metabolic syndrome). To do any less would be to perform a grave disservice to our patients.

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