ANTIPSYCHOTIC DRUGS: Sudden Cardiac Death Among Elderly Patients

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ABSTRACT

Sudden cardiac death has become a significant clinical concern when prescribing antipsychotic drugs, especially to older people with dementia. Sudden death syndrome has been known for decades to occur in association with taking first-generation antipsychotic medications, but it has become more prominent recently due to safety reviews about the use of second-generation antipsychotic medications. In 2005, the United States Food and Drug Administration disseminated information about cardiac fatalities, which led to black box warnings in second-generation, antipsychotic, drug-prescribing literature about higher mortality when administering to elderly persons with dementia-related psychoses. In this population, treatment results in death rates of 4.5 percent, as compared to 2.6 percent in subjects taking a placebo. Actually, patients treated with both the first- and second-generation versions experienced an increased incidence of fatalities. Before utilizing these agents, a careful workup must be completed. The presence of a psychosis or mania should be the only conventional indication for prescribing first- and

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second-generation antipsychotic medications. Physicians should always evaluate patients for comorbid conditions, especially heart disease and metabolic abnormalities, and all currently used medications to assure a risk-to-benefit ratio favoring the application of an antipsychotic medication. An electrocardiogram is a part of the evaluation of the cardiac status and determines the base line QT interval. While prescribing these medications in elderly patients, physicians must provide individualized clinical, electrocardiographic, and pharmaceutical monitoring.

INTRODUCTION

The number of people over age 65 is expected to double by the middle of the next century.[1] In the mid-1900s, elderly persons accounted for one in eight Americans, with estimates that they will comprise one out of five of the population by 2030. Those over age 85 could become the fastest growing group.

Antipsychotic drugs are widely utilized.[2] There is a concern about the safety of prescribing them, especially to older patients with dementia. Sudden cardiac death while on these medicines has long been known,[3,4] but is currently a more active issue in pharmacotherapy practice. It is now established that taking first- and second-generation antipsychotic drugs induces an almost two-fold increase in patient mortality rates in patients over age 65, as compared to people on a placebo.[5–8] The newer, second-generation antipsychotic medication literature now contains a "black box" warning noting that "increased mortality in elderly patients with dementia-related psychosis" is documented when older people with dementia are treated with such agents.[9] This concern has precipitated changes in the way these medications are prescribed.

ANTIPSYCHOTIC MEDICATIONS

When considering an antipsychotic drug, especially in elderly persons, attention must be directed to the detection of medical comorbidities and knowledge about other medications the patients might be taking. Physicians should especially consider heart disease, with conduction delays, congestive failure, or rhythm disturbances, and also metabolic abnormalities, such as hypocalcemia, hypomagnesemia, hypokalemia, hypoglycemia, or hypothyroidism. Physicians should be more cautious with patients who are coprescribed medications that lengthen the cardiac cycle QT interval, such as procainamide, amiodarone, or amitriptyline, since this increases the chances for dangerous arrhythmias. A thorough evaluation includes a risk-to-benefit ratio assessment that considers the indications for using an antipsychotic medicine. Psychoses or manias are the primary conditions for which these drugs are prescribed. They have been also administered for the treatment of depression, anxiety, insomnia, and impulsive or assaultive behaviors; yet, especially in this older population, they are now usually restricted only to therapy of a psychosis or mania. Physicians must consider the side-effect profile and adverse-consequence potential of the proposed drug, the patient's psychiatric or medical conditions, and concurrent medications or substances used by the patient. A history, vital signs, and physical examination, with emphasis on cardiopulmonary and neurologic parameters, and an electrocardiogram are a part of this pretreatment evaluation. Also, the physician should screen for diabetes, hyperlipidemia, weight, general health, electrolyte or other metabolic disturbances, renal function, and hepatic status. Further diagnostic tests are indicated on a clinical basis as follows: a chest x-ray is obtained if congestive failure or pneumonia is in the differential, a stress test may be done if ischemia is an active problem, and an echocardiogram can depict functional cardiac pathologies (Table 1).

For decades, antipsychotic drugs have been associated with an increased risk of sudden death, which has been documented in recent studies.[10] In April 2005, the United States Food and Drug Administration (FDA) announced that patients with dementia-related psychosis treated with second-generation antipsychotic drugs are at an increased risk of death.[9] A similar risk also applies to first-generation antipsychotic medicines as well;[5–7] this fact was already long known to physicians from clinical experience. The pathophysiology may be related to blocking repolarizing potassium currents *in vitro* and to prolonging the cardiac cycle's QT interval, which is implicated in ventricular arrhythmias (Table 2).[11]

In addition to arrhythmias, other proposed mechanisms for sudden death include the following: 1) peripheral vasodilation leading to cardiovascular collapse,[12] 2) congestive failure,[5] 3) respiratory dyskinesia with asphyxia,[13] 4) oral-laryngeal-pharyngeal dystonia with airway obstruction,[14] 5) acute myocarditis or cardiac myopathy,[15] and 6) infections (e.g., pneumonia).[5] Infections increase mortality whether related to pharmacotherapy or not or when sedation and extrapyramidal muscular dysfunction results in aspiration. It is well accepted that antipsychotic drugs pose a cardiac risk to elderly persons; yet, attention has focused particularly on patients with dementia-related psychosis.[9] These medications have long been utilized and are still often prescribed to diminish psychotic thinking or grandiose behaviors in people with dementia.

Beside cardiac concerns, antipsychotic drugs appear to escalate the risk for cerebrovascular events like syncope and stroke.[7,16] Reportedly, there is a 50-percent rise in such adversities among geriatric subjects with dementia when treated with either the first- or second-generation agents.[17] The mechanism remains unknown. Less prominently, there is also research that reports

contrary evidence of no increase in adverse medical outcomes for people on both types of antipsychotic medications.[18]

Antipsychotic drugs remain, however, an important pharmacotherapy for older people with schizophrenia,[19] mania, and other psychoses. They are usually prescribed when a psychosis is evident and yields dysfunction.[20] Indications sometimes include mania or agitation; however, they are now less often recommended for treating nonpsychotic conditions like depression, nausea, pain, insomnia, or anxiety disorders. Doctors should also avoid them in cases of delirium, preferring more etiologically targeted therapies, (e.g., fluid restriction in hyponatremia or oxygenation for hypoxic cases). Due to cardiovascular concerns, prescribing antipsychotic medications to older persons with dementia has been reduced in cases lacking specific indications, but for individuals with overt psychoses they are still a first-line therapy. Many psychotic patients will meet criteria for treatment with these medicines.[20] Even though antipsychotic drugs can be useful in treating depression, their use in individuals with dementia should be limited.

In the absence of psychosis, conventional pharmacotherapy options, like anti-anxiety medicines or mood stabilizers, are utilized.[20] Other pharmaceuticals, such as antidepressants, antihistamines, and for dementia cases, cholinesterase inhibitors or an N-methyl-D-aspartate receptor agonist, are used for routine indications. Physicians should also consider applying nonmedicinal therapies like psychotherapy, exercise, or socialization.[7]

TABLE 1. Evaluation and monitoring antipsychotic drugs in elderly patients

History	Inquiry about medical conditions, drug allergies, cardiopulmonary diseases, renal/hepatic or other dysfunctions, metabolic abnormalities, pharmaceutical treatments, substances used, and current health status
Physical examination	Special focus on cardiopulmonary status
Electrocardiogram	To assess cardiac interval durations (e.g., QT interval), rhythm, heart size, and for ischemia
Chest X-ray	To check for congestive failure or pneumonia
Stress test	To evaluate for coronary artery ischemia
Echocardiogram	To assess cardiac function and pathology

TABLE 2. Degree of QT prolongation by selected antipsychotic medication[21,23,24,30]

RANGE	FIRST GENERATION DRUGS	SECOND GENERATION DRUGS
Higher	Thioridazine	Ziprasidone
Mid-range	Chlorpromazine	Quetiapine
Low	Haloperidol	Risperidone Clozapine Olanzapine Aripiprazole

SUDDEN CARDIAC DEATH

Torsades de pointes may explain the sudden death associated with the use of antipsychotic drugs. Other dangerous rhythm disturbances may also occur. A prolonged QT interval predisposes to arrhythmias.[21] Since the QT interval is rate dependent, a longer duration QT may be normal at a slow pulse, while the corrected QT (QTc) interval, which accounts for the heart rate, is the more accurate predictor of concern. A prolonged QTc is an overtly known risk factor for sudden death, and these medications lengthen the QT interval. A normal QTc is 390±40 milliseconds. Durations over 440 milliseconds warrant greater concern, and values over 500 milliseconds heighten the probability of dangerous or fatal rhythm disturbances.

The risk of sudden death when prescribed first-generation antipsychotic drugs increases with age (rates of 2, 19, or 27 per 10,000 person-years for patients aged 15–44, 45–64, or 65–84 years, respectively).[4] Second-generation antipsychotic agents induce a near doubling in the rate of death among elderly patients with dementia at a 4.5-percent mortality rate, versus 2.6 percent for those on placebo.[6] While the relative risk is much increased, the absolute risk remains less significant. The cardiac danger is also medication dose-dependent and increases in cases with previous cardiovascular conditions.[4] During treatment, the physician should repeat the electrocardiogram periodically to determine whether the drug has induced precarious degrees of QT prolongation. The frequency to review the tracing is an individualized case-by-case clinical decision based on patient health, past QT durations, pharmaceuticals applied, and drug dosages.

Thus, patients taking either first- or second-generation antipsychotic drugs have nearly a two-fold increase in the likelihood of sudden cardiac death, and both medication classes evidence an escalating risk at higher doses.[5–8] Sudden death also increases with age among geriatric populations.[22] Research documents that the degree of increase in risk is significant and of great clinical relevance, but the occurrence rate of fatalities remains low.[4,6] Some investigators suggest that the newer generation antipsychotic drugs may be safer than the older ones,[5,7] but this remains to be clarified. It is also important to note that an overt psychosis diminishes quality of life and when untreated, psychosis carries significant health risks.

Among the first-generation antipsychotic drugs, thioridazine induces the greatest QT prolongation, but chlorpromazine, haloperidol, and others can influence the timing as well.[21,23] Ziprazidone is the second-generation agent most noted for QT changes, yet the other medications may induce lesser degrees of lengthening. Aripiprazole might be the only one of these that is less likely to influence the QT duration.[24] Better understanding about the QT influence of the newest drugs, paliperidone and asenapine, will be clearer once they are utilized over a longer period of time. Previous use of antipsychotic medication does not influence QT durations after the drug is stopped.[21]

COMORBIDITY

Coexisting medical conditions and other factors also increase the susceptibility to adverse effects of antipsychotic agents. Coronary artery ischemic disease is the main pathology of concern and is especially severe in persons with chronic mental illness.[25] The incidence of diabetes mellitus is higher and thus escalates the rates for cardiac illnesses and renal failure. This is worsened by antipsychotic drug-induced metabolic syndrome, which results in weight gain, hypertension, hyperlipidemia, and a powerful diabetogenic influence. Little preventive care and lower-quality medical treatment for these patients confers an elevated prevalence of significant heart disease.[26,27] This also might be related to less healthcare availability, financial or other restrictions to medical system access, and patient adherence or poor judgment issues. Negative physician attitudes and patient inability to afford various interventions add to these problems. Additional important factors include smoking, obesity, inactivity with a sedentary life style, and nutritional deficiencies or diets high in fats and calories.

In a study of geriatric subjects with acute myocardial infarction, with or without psychiatric conditions, those with mental illness received less effective therapies and experienced a 19-percent higher mortality.[28] The lack of appropriate care may account for some of these early fatalities. Electrolyte imbalance, congestive heart failure, renal or hepatic disease, prescribed polypharmacy, and substance abuse also escalate susceptibility to death or arrhythmias when people are receiving antipsychotic drugs. Among nursing home residents with dementia, all-cause mortality rates were elevated for those on antipsychotic medicines.[29]

CONCLUSION

Before prescribing an antipsychotic medicine to elderly persons, physicians must determine a risk-to-benefit ratio that accounts for the danger of sudden death. Each individual appraisal includes a review of potential contributing factors, like heart disease, patient age, general health, drug abuse, and other medications used. The urgency of selecting an antipsychotic drug or an alternate option is important in such an evaluation; prescribing assumes an assessment that evidences an expectation for a positive benefit.[7] Physicians should avoid using antipsychotic drugs in nonpsychotic cases when indications are not clearly evident, especially in older, ill patients.

Antipsychotic medications still have an important role in geriatric patients and are required for optimal care in selected psychotic or manic patients, sometimes even for those with dementia-related psychoses. Regarding specific drug choice, it is important to note that both older and newer antipsychotic medication groups can, on rare occasions, induce sudden death. The newer-generation pharmaceuticals, though safer for neurological complications, may be less safe in this cardiac dimension than originally considered. Always evaluate as to whether confounding comorbid conditions or risk factors exist. Explain to patients and family members the pros and cons of using these medicines before beginning and during therapy.

When prescribing antipsychotic medications, always start at a low dose and gradually titrate up to the lowest effective, well-tolerated amount. Note any new pathologies and medications the patient may be taking. QT prolongation is important, but it alone is not a sufficient marker to determine the total risk of developing an arrhythmia. Nevertheless, electrocardiographic monitoring is recommended before and during treatment, based on clinical parameters. It is important for physicians to follow vital signs, weight, and metabolic laboratory studies of blood glucose, lipids, electrolytes, and renal/liver functions. Further individualized laboratory testing is repeated if clinically indicated. Concerns about this adverse effect are high and risk exists; however, arrhythmias and/or cardiac deaths are actually uncommon.

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