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Antidepressants and Atrial Fibrillation:

The Importance of Resourceful Statistical Approaches to Address Confounding by Indication

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Antidepressant drugs are known to influence cardiac conduction, and there are theoretical grounds to suggest that serotonin reuptake inhibition by antidepressants may predispose to AF. A large register-based cohort study found that antidepressant use was associated with an increased risk of AF during the first month following antidepressant initiation. Whereas this may seem alarming, additional analyses found that the risk progressively diminished in succeeding months. Further analysis showed that antidepressant use was associated with an even higher risk of AF in the month before antidepressant initiation; this finding implies that patients who initiate antidepressant drugs are already at increased risk of AF and that the significant association between antidepressant drug use and AF might be because of confounding by indication. In other words, the indication for antidepressant use rather than antidepressant use, itself, may be the risk factor for AF, and this risk is probably state-dependent because it diminishes with the passage of time, during which period the indication for antidepressant use presumably resolves. In another study, which used a nested case-control design, current and recent users of antidepressant drugs were contrasted not with antidepressant nonusers but with past users of antidepressants. The study found that neither current nor recent users were at increased risk of AF. This again indicates that antidepressants are unlikely to directly predispose to AF. In both studies, the possibility of confounding by indication was addressed by resourceful statistical approaches to the research question. Such resourcefulness in analysis is necessary in all observational studies of the association between an exposure and an outcome. In the absence of efforts to address confounding by indication, an identified association between an exposure and an outcome should not be presumed to reflect a cause-effect relationship.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia; the population prevalence is 2.3%–3.4%, and the lifetime prevalence is 1 in 4.^{1,2} AF is associated with impaired quality of life, increased health care expenditure, and increased hospitalizations. AF is also associated with acute coronary syndromes, ischemic stroke, and cardiac failure. Finally, AF is associated with an up to 2-fold risk of death.¹

Atrial Fibrillation: Risk Factors

Risk factors for AF include genetic susceptibility, older age, male sex, European ancestry, sedentary lifestyle, smoking, obesity, diabetes mellitus, obstructive sleep apnea, high blood pressure, and others.³ Drugs have also been associated with AF, particularly acute AF, and drug-induced AF may be undiagnosed. In fact, a large number of cardiovascular and noncardiovascular drugs are known to affect cardiac autonomic tone and cardiac electrophysiology, and the effect of these drugs on the risk of AF is increased in the presence of other risk factors for AF.⁴ Drugs implicated in the risk of AF include cardiac stimulants, vasodilators, antiarrhythmics, diuretics, cholinergic agents, xanthine alkaloids, cancer chemotherapy treatments, corticosteroids, and many others,^{4–6} though a cause-effect relationship is not established for most of the drugs.

Antidepressants, especially tricyclic antidepressants, are known to influence cardiac conduction. These drugs have been associated with an increased risk of QTc prolongation and of cardiac arrhythmias.^{7–10} Serotonergic antidepressants may particularly predispose to AF through action on 5-HT₄ receptors, increase in intracellular calcium, and increase in the amplitude of the pacemaker current in atrial myocytes.¹¹ So might antidepressants be associated with an increased risk of AF? This possibility was recently examined in 2 observational studies.^{11,12} These studies show that antidepressant use is a marker for the risk of AF rather than a direct risk factor for AF. These studies also illustrate how investigators can be resourceful in addressing confounding by indication when examining associations between treatments and adverse outcomes in nonrandomized studies.

Antidepressants and Atrial Fibrillation: The Danish Data

In a nationwide Danish register-based study,¹² a cohort of 785,254 adults was identified to have redeemed a prescription for antidepressant medication. These antidepressant users were matched 1:5 with a reference group of antidepressant

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nonusers, based on sex and age at antidepressant initiation. Both groups had no prior history of AF; the month before recruitment was exempted from this requirement. Both groups also had no history of valvular heart disease. Finally, both groups had no prior exposure to antidepressants.

Two-thirds of the sample was below age 60 years. The sample was 59% female. Citalopram was the commonest antidepressant, used by 47% of patients. Another 30% of patients used other selective serotonin reuptake inhibitors (SSRIs), most commonly escitalopram. Mirtazapine was used by 15% of patients.

In an analysis that adjusted for a large number of sociodemographic and clinical confounds, antidepressant use was associated with a trebled risk of AF during the first month following antidepressant initiation (hazard ratio [HR], 3.18; 95% confidence interval [CI], 2.98–3.39). On the surface, this finding seems alarming. However, in further analysis, this risk was found to attenuate during months 2–6 after antidepressant initiation (HR, 1.37; 95% CI, 1.31–1.44) and it further attenuated during months 6–12 after antidepressant initiation (HR, 1.11; 95% CI, 1.06–1.16).

Importantly, the risk of AF was elevated to an even greater magnitude in antidepressant users during days 1–15 *before* antidepressant initiation (HR, 4.29; 95% CI, 3.94–4.67) and days 16–30 *before* antidepressant initiation (HR, 7.65; 95% CI, 7.05–8.30). The findings were similar in sensitivity analyses. Because antidepressants cannot cause AF before they are started, the implication here is that antidepressant use is only a marker for the risk of AF; the indication for the antidepressant, or characteristics of patients for whom antidepressants are prescribed, may be the risk factor(s). The risk factors are probably related to depression and are state-dependent; this is a reasonable supposition given that the risk progressively attenuated with the passage of time, no doubt in parallel with the resolution of the indication for which the antidepressant was prescribed.

Antidepressants and Atrial Fibrillation: The UK Data

The data for this nested case-control study¹¹ were drawn from the UK Clinical Practice Research Datalink, a nationally representative, primary care database that contains medical records of > 13 million people. The cohort comprised adults (n = 116,125) who had newly started treatment with an antidepressant drug for a diagnosis of depression (55%) or anxiety (45%); those with a past history of a cardiac condition were excluded. Cases (n = 1,271) comprised patients with incident chronic AF. For each case, up to 10 controls were identified with matching based on age, sex, year of cohort entry, and duration of follow-up. The mean age of the sample was 72 years. The sample was 37% female.

Current use of antidepressants was defined as receiving a prescription for an antidepressant during the 6 months before the occurrence of AF. Recent use was defined as receiving a last antidepressant prescription 6–12 months before the AF. Past use was defined as receiving the last prescription for an antidepressant > 1 year before the AF. Analyses were adjusted for risk factors for AF.

Relative to past use of antidepressant drugs, neither current use (RR, 0.98; 95% CI, 0.86–1.12) nor recent use (RR, 1.02; 95% CI, 0.86–1.30) was associated with an increased risk of AF. In secondary analyses, no antidepressant class and no category related to potency of serotonin reuptake inhibition was associated with an increased risk of AF. In further analyses, cumulative use of antidepressants, medication adherence, and individual antidepressant drugs were also not associated with an increased risk of AF. Finally, when the exposure window for current use was reduced to 3 and then to 2 months, the findings remained unchanged.

In conclusion, whereas this study¹¹ did not examine whether the risk of AF was higher in antidepressant users relative to nonusers, it did show that current and recent antidepressant use did not increase the risk of chronic AF (relative to past use) in patients who received these drugs for depression or anxiety.

Observational Research in Other Fields

Investigators are taking increasing precautions, now, to guard against spurious associations. For example, in a 10-year prospective study¹³ of a Canadian cohort (n = 6,645) of men and women aged 50+ years, SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) drugs were associated with an increased risk of fragility fractures (HR, 1.88; 95% CI, 1.48–2.39) relative to nonusers. The risk remained significant even after adjusting for a large number of risk factors, including those related to medical comorbidity, bone mineral density, and history of previous falls. The authors concluded that their findings supported the association between SSRI/SNRI use and fragility fractures.¹³ A recent Swedish register-based study¹⁴ (n = 408,144) also found an increased risk; the incidence of hip fracture was 3.5% vs 1.3% in antidepressant users vs nonusers during the year after initiating antidepressant medication. However, in the same study, the risk was 2.8% vs 1.1% in users versus nonusers for the year *before* initiating antidepressant medication. In fact, in adjusted analyses, the highest odds of fracture were during the period 16–30 days *before* initiating antidepressants (OR, 5.76; 95% CI, 4.73–7.01).¹⁴ Antidepressants clearly cannot increase the risk of hip fracture before treatment initiation; therefore, the risk of fracture is more likely to lie with the illness (and its correlates) for which the drug was prescribed.

In another context, meta-analyses have demonstrated that antidepressant exposure during pregnancy is consistently associated with an increased risk of autism spectrum disorder (ASD) in the offspring. However, this risk is attenuated after adjusting for confounding variables; the risk falls short of statistical significance after adjusting for maternal mental illness; and the risk is elevated even when antidepressant exposure occurred only during the preconception period, when medications could not possibly have directly affected the child.¹⁵ Studies also show that the risk of ASD is elevated after paternal exposure to antidepressants and in siblings (of ASD probands) who have not been exposed to antidepressants during pregnancy.¹⁶ These findings indicate that the risk of ASD following antidepressant exposure during pregnancy is

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likely to lie with correlates of maternal depression and the severity thereof rather than with the use of medications to treat the depression.

Conclusions

The examples reviewed in this article indicate that, in observational studies, treatments may be found to be associated with many adverse outcomes, but if authors are resourceful in their choice of control groups, or in their selection of targets for secondary analyses, confounding by indication may emerge as an explanation for the identified association between treatment and adverse outcome. Resourcefulness in analysis is an important requirement in all observational studies that investigate the association between an exposure and an outcome. When authors do not adequately address confounding by indication, an identified association should not be presumed to reflect a cause-effect relationship. Interested readers are referred to an earlier article in this column that considered confounding and the limitations of observational studies.¹⁷

Parting Notes

SSRI antidepressants are associated with an increased risk of bleeding events through several different mechanisms; the risk is further elevated in patients receiving anticoagulant medications.^{18,19} Patients with AF receive anticoagulant treatment. SSRIs have been shown to increase the risk of bleeding events in patients with AF who are receiving anticoagulants.²⁰

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