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Antidepressants, Mood Stabilizers, Antipsychotics, and the Risk of Cataract

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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

Cataract is a common disease of the eye, and depression is common in patients with cataract. This raises the possibility that depression and the drugs used to treat depression may be risk factors for cataract. In a recent systematic review and meta-analysis of 7 case-control studies with a pooled sample of 447,672 cases and 1,510,391 controls, antidepressant drugs were associated with a very small but statistically significant increase in the risk of cataract; the odds ratios for different classes of antidepressants were in the 1.12–1.19 range. None of the 7 studies in the meta-analysis adjusted their analyses for confounding by indication. Furthermore, the meta-analysis results were characterized by unexplained high heterogeneity, and there was evidence suggestive of publication bias. These data, therefore, do not make a sufficient case for antidepressants being causal for cataract. Rather, the antidepressant data, along with data that associate mood stabilizer exposure with the risk of cataract, suggest that major mental illness and the correlates thereof may be a risk factor for cataract rather than the drugs that are used to treat these disorders. Surprisingly, in similar research designs, antipsychotic drugs were found either to have no effect or to protect against incident cataract. This indicates that the relationship between antidepressant exposure and cataract merits closer investigation, using research designs and analyses that better address confounding by indication. Examples for such research designs and analyses are provided. Until stronger evidence becomes available, a cause for concern remains unestablished.

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Depression and Eye Diseases

Zheng et al¹ described a systematic review and meta-analysis of depression and depressive symptoms in patients with eye diseases. They identified 28 relevant studies (pooled N=6,589) and estimated that the prevalence of depression or depressive symptoms was 25% (95% CI, 20%–30%) in the pooled sample. The highest prevalence was found in patients with xerophthalmia (29%). The prevalence was also high in patients with glaucoma (25%), age-related macular degeneration (24%), and cataract (23%). Patients with eye disease were at higher risk of depression or depressive symptoms than healthy controls (odds ratio [OR], 1.59; 95% confidence interval [CI], 1.40–1.81).

It is possible that the depression in patients with eye disease is a reaction to the ocular symptoms, and it is possible that the depression and eye disease occur coincidentally. It is also possible that depression and its correlates are a risk factor for at least some eye diseases. In this context, one possibility is that the antidepressant drugs used to treat depression increase the risk of cataract.

Cataract

Cataract is a disease of the eye that is characterized by impairment of vision resulting from the development of opacities in the lens. Cataract is the leading cause of blindness in low and middle income countries. The prevalence of cataract is about 4% in persons who are around 60 years of age and >90% in those who are 80 years and older. Risk factors for cataract include older age, female sex, genetic vulnerabilities, lifestyle behaviors, medical comorbidities, and many others.²

Psychotropic drugs, particularly antidepressant drugs, have recently been associated with cataract. This article critically examines the literature on the subject.

Antidepressant Drugs and Cataract: Meta-Analysis

Fu et al³ described a systematic review and meta-analysis of studies that examined the development of cataract after antidepressant use. They searched electronic databases, reference lists, and other sources and identified 7 relevant case-control studies; 3 had been conducted in the United States, 2 in Canada, and 1 each in the United Kingdom and Taiwan. The pooled sample included 447,672 cases and 1,510,391 controls.

Important findings from the meta-analysis³ are presented in Table 1. In short, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants were each associated with a small but statistically significant increase in the risk of cataract. All 3 analyses were characterized by substantial heterogeneity; the authors did not examine the source of the heterogeneity. Among individual antidepressant drugs, the risk was significant for citalopram, fluoxetine, fluvoxamine, and venlafaxine but not for paroxetine, sertraline, escitalopram, duloxetine, and milnacipran; it is possible that many analyses were underpowered for the individual drugs. Visual inspection of the funnel plot suggested clear publication bias.

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Table 1. Antidepressant Use and the Risk of Cataract^a

1. Selective serotonin reuptake inhibitor antidepressants were associated with an increased risk of cataract (6 studies; OR, 1.12; 95% CI, 1.06–1.19; $I^2 = 92\%$).
2. Serotonin-norepinephrine reuptake inhibitor antidepressants were associated with an increased risk of cataract (4 studies; OR, 1.13; 95% CI, 1.04–1.24; $I^2 = 68\%$).
3. Tricyclic antidepressants were associated with an increased risk of cataract (3 studies; OR, 1.19; 95% CI, 1.11–1.28; $I^2 = 58\%$).

^aData are from the meta-analysis by Fu et al.³

Abbreviations: CI = confidence interval, OR = odds ratio.

The studies in the meta-analysis suffered from important limitations. One study⁴ did not adjust the analyses for any confounding variable. One study examined the association between antipsychotic use and cataract,⁵ and another examined the association between statin use and cataract⁶; adjusting for confounding variables related only to the primary analyses and not to the context of antidepressant use. Of the remaining 4 studies, only 1 undertook propensity score matching⁷; the rest^{8–10} adjusted only for a few cataract risk factors. In other words, if depression and the correlates thereof are a risk factor for cataract, confounding by indication was not addressed in the studies that were subjected to meta-analysis.

The meta-analysis³ and its findings were characterized by many limitations. The source of the heterogeneity was not identified, and so biasing influences remain unknown. The funnel plot showed clear publication bias, and so the inclusion of the hypothetical unpublished studies could make the already small ORs smaller and nonsignificant. Cataract is a common condition, and so the ORs computed in the meta-analysis could overestimate the risks.¹¹ Finally, there are concerns about how the authors extracted the data. For example, the values for the OR and the 95% CI presented for one study could not be identified in the original paper⁴; it is possible that the authors of the meta-analysis³ pooled data for different types of cataract, but this information was not provided.

In summary, whereas the meta-analysis³ suggested that there is a very small association between antidepressant use and cataract, all that can be concluded from the data is that antidepressant use is a marker of risk rather than a risk factor for the disease.

Antidepressants and Cataract: Other Recent Findings

In a population-based, nested case-control study conducted in patients with schizophrenia, Chou et al¹² examined the association between antipsychotic drug use and a new diagnosis of cataract; analyses were adjusted for confounding variables, and antidepressant use was one such confounding variable. In the adjusted analysis, concurrent antidepressant use was associated with an increased risk of cataract (OR, 1.30; 95% CI, 1.09–1.55).

In another population-based, nested case-control study conducted in patients with bipolar disorder, Chu et al¹³ examined the association between antipsychotic drug use and a new diagnosis of cataract; analyses were adjusted for

confounding variables, and antidepressant use was one such confounding variable. In the adjusted analysis, concurrent antidepressant use was associated with an increased risk of cataract (OR, 1.23; 95% CI, 1.06–1.43).

In both of these studies,^{12,13} as well as in 2 of the studies^{5,6} included in the meta-analysis by Fu et al,³ the association between antidepressant use and cataract was not the primary objective of the study. However, all 4 studies adjusted the analyses for cataract risk factors, and so the ORs for the association between antidepressant use and cataract were also adjusted ORs.

The above notwithstanding, there are 2 important reasons why the research design would not have been satisfactory for studying the effects of antidepressant exposure in any of these 4 studies. One is that antidepressants are prescribed mainly for depression and anxiety, and, for example, a study examining the association between statin use and cataracts⁶ would not have adjusted for depression- or anxiety-related confounds. The other is that when antidepressant exposure was not the variable of interest, analyses such as current vs past exposure, long-term vs brief exposure, and so on, would not have been performed.

Mood Stabilizers and Cataract

In a population-based, nested case-control study conducted in patients ($n = 14,288$) with bipolar disorder and schizophrenia, Chu et al¹⁴ examined the association between mood stabilizer use and a new diagnosis of cataract; analyses were adjusted for confounding variables, including medical and ophthalmic comorbidities, drugs known to increase the risk of cataract, and health care utilization in the past year.

Relative to no use of mood stabilizers, only use for > 2 years was associated with an increased risk of cataract (OR, 1.14; 95% CI, 1.01–1.29), and only when the dose was 0.5 defined daily doses or greater (OR, 1.28; 95% CI, 1.08–1.53). Among the mood stabilizers, > 2 years of use of valproate, carbamazepine, and lamotrigine in monotherapy were not associated with increased risk of cataract; however, use of lithium for > 2 years, with (OR, 1.44; 95% CI, 1.13–1.85) or without (OR, 1.39; 95% CI, 1.01–1.92) other drugs, and use of valproate for > 2 years along with other drugs (OR, 1.26; 95% CI, 1.02–1.57) were both associated with an increased risk.

The authors¹⁴ suggested that the nonsignificant results with carbamazepine and lamotrigine may have been related to small sample sizes in these subgroups.

Antipsychotic Drugs and Cataract

At least 3 studies have recently examined the association between antipsychotic drug exposure and cataract. Pakzad-Vaezi et al⁵ described a nested case-control study that included 162,501 patients with cataract and 650,004 age- and date-matched controls. In analyses that adjusted for cataract risk factors, including antidepressant use, typical (rate ratio [RR], 0.88; 95% CI, 0.81–0.96) and atypical (RR, 0.80; 95% CI, 0.77–0.84) antipsychotic drug exposure were

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both associated with a lower risk of cataract. The benefit appeared dose-dependent: the RR was 0.85 in patients who had filled 1–6 prescriptions and 0.70 in those who had filled >6 prescriptions.

In another nested case-control study, Chou et al¹² age-, sex-, and date-matched 2,144 schizophrenia patients with cataract with 2,222 controls. In analyses that adjusted for cataract risk factors, they found that there was no significant association between drug exposure and cataract for any of 9 atypical antipsychotics. This study, however, compared continuous with past users of antipsychotics to address confounding by indication, in contrast with studies that compared users with nonusers.

Chu et al¹³ examined the relationship between antipsychotic use and cataract in bipolar disorder patients. This was also a nested case-control study with 1,684 cases and 1,608 age-, sex-, and date-matched controls. In analyses that adjusted for cataract risk factors, past (OR, 0.74; 95% CI, 0.62–0.89) and continuous (OR, 0.71; 95% CI, 0.59–0.85) atypical antipsychotic use were both associated with a reduced risk of cataract. There was no significant association between typical antipsychotic exposure and the risk of cataract.

Critical Evaluation

The data reviewed indicate that both antidepressant drugs and mood stabilizers are associated with a small but significantly increased risk of cataract. Therefore, if major mental illness and its correlates are confounds that explain the association, a significantly increased risk should be demonstrable for antipsychotic drug exposure, as well. However, no such risk has been demonstrated; in fact, if anything, antipsychotic drugs seem to confer protection against cataract.

This is a puzzling situation and one that indicates that the relationship between antidepressant drugs and cataract needs to be explored through resourceful means, as has been done in the context of antidepressants and the risk of atrial fibrillation¹⁵ and antidepressant exposure during pregnancy and the risk of autism spectrum disorder (ASD) in the offspring.^{16,17} Suggestions for future research are provided in the next section.

Antidepressants and Cataract: Suggestions for Future Research

Confirming the findings of the reviewed studies using information from other databases will serve no purpose; if confounding by indication is present in the existing studies, it will also be present in future studies. What is necessary, therefore, is a better approach to research design and data analysis.

At the simplest level, in addition to adjusting for cataractogenic risk factors, future studies should attempt to adjust analyses for confounds related to depression and the severity thereof; the latter was done in exemplary fashion, for example, by Rai et al¹⁸ in the context of gestational exposure to antidepressants and the risk of ASD in the offspring.

Propensity score matching is another important statistical approach that may be considered.¹⁹

Investigators need to be resourceful in their choice of control analyses. If depression is a confound, then the association between antidepressants and cataract should be stronger in moderate to severe depression than in mild to moderate depression. Studying the risk in patients who receive cognitive-behavioral therapy but not antidepressants may be instructive if an increased risk of cataract is found; however, an absence of increased risk does not eliminate an association between depression and cataract because depression that is not severe enough to necessitate antidepressant drug use may not be severe enough to be associated with cataractogenic correlates.

If antidepressants are causally associated with cataract, then the association should be demonstrable in all diagnostic subgroups, including patients with anxiety, obsessive-compulsive disorder, and schizophrenia. Because cataract does not develop overnight, if antidepressant use is causal for incident cataract, then current exposure should be associated with higher risk than past exposure; the risk should increase with increasing duration of exposure; and higher doses should be associated with greater risk. Unexposed sibling analyses or the adjustment for family history as a risk factor could be useful because genetic influences are known in cataract.

Finally, given that cataract, depression, and antidepressant exposure are all common, studies need to examine what the population attributable risk may be in the worst case scenario.

Conclusions

The data associating antidepressant drug use with incident cataract were obtained from studies that were methodologically unsuited to suggesting a cause-effect relationship; therefore, confounding by indication could be a possible explanation for the findings. The association of mood stabilizer exposure with the risk of cataract strengthens the supposition that major mental illness and the correlates thereof may carry the risk for cataract rather than the drugs used to treat these conditions. However, antipsychotic drug exposure in similar research designs was found to have a protective effect against cataract in both schizophrenia and bipolar patients. This suggests that the relationship between antidepressant drugs and cataract merits further investigation. However, the data, as they stand, are not sufficiently convincing to justify warning patients against the use of antidepressants with cataract as the outcome of concern.

Parting Notes

In the studies reviewed, various authors described hypothetical mechanisms through which different drugs may predispose to or protect against the risk of cataract. These mechanisms are speculative and are not considered in this article because the clinical significance of a mechanism can be established only by clinical evidence.

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