

## Drug review

# Psychotropic medication and cataract: a review of case-control studies

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## Abstract

Ocular side effects are possible to occur as side effect of psychotropic drug treatment. Antidepressants and typical antipsychotics have been associated with increased intraocular pressure, glaucoma, lenticular pigmentation, visual disturbances and cataract, whereas the risk of atypical antipsychotics and mood stabilizers remains unclear. The aim of our study was to review the case-control studies assessing the risk for cataract of three major classes of psychotropic medication: antidepressants, antipsychotics and mood stabilizers. Four studies assessed the risk of antidepressant drugs. A higher risk for cataract diagnosis or surgery was observed in three studies, especially on long-term use of antidepressants. One study could not identify a higher risk of antidepressant use in general, yet a higher risk was observed in patients younger than 65 years. Different types of antidepressant seem to carry different risks, with proposed harmful effects of dual mechanism and intermediate SERT affinity. Three studies suggested that the association of atypical antipsychotics and high potency typical antipsychotics with cataract is unlikely, or even that atypical antipsychotic drugs might be protective against cataract. However, there is inconsistency between the sparse preclinical and clinical evidence of their protective and harmful effects. Only one study suggested a possible association of mood stabilizers with cataract, despite the discrepant results on individual drugs. Concluding, these case-control studies cannot establish a harmful or protective causal relationship between psychotropic medication and development of cataract. Further research is needed in order to provide proper recommendations.

**Keywords:** antidepressants, antipsychotics, mood stabilizers, cataract.

## Introduction

Cataract is a common cause of visual impairment with significant health consequences. Several risk factors may be associated with cataract, such as increased age, female gender, smoking, unhealthy lifestyle, diabetes mellitus, hypertension and other physical comorbidities, as well as ophthalmic comorbidities, family history of cataract and increased exposure to ultraviolet radiation. Certain drugs seem to predispose to cataract, such as systemic steroids, beta adrenergic antagonists, statins, cholinesterase inhibitors and possibly some psychotropics [1]. Antipsychotic and antidepressant medication targets mainly neurotransmitter receptors and transporters, which along with other mechanisms could play important roles in ocular physiology and cataract development [2]. Ophthalmic events, such as increased intraocular pressure, glaucoma, cataract and visual disturbances have been associated with antidepressants [3]. Typical antipsychotics, especially phenothiazines, have been associated with lenticular pigmentation and cataract, whereas the risk of atypical antipsychotics and mood stabilizers is questioned [4, 5]. As a result, psychotropic medication, i.e. antipsychotics, antidepressants and mood stabilizers, might be modifiable factor for cataract development. Herein, the most recent case-control studies of the risk of psychotropic medication for cataract development are reviewed and discussed.

## Search strategy

A literature search was conducted on PubMed (21/12/2017) using the keyword cataract combined with antidepressants (antidepressant, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine, amitriptyline, amoxapine, desipramine, dosulepin, doxepin, clomipramine, imipramine, maprotiline, nortriptyline, protriptyline, tianeptine, trimipramine, isocarboxazid, metralindole, moclobemide, phenelzine, pirlindole, selegiline, tolaxatone, tranlycypromine, mianserin, mirtazapine, vilazodone, vortioxetine, agomelatine, buspirone, bupropion, reboxetine, nefazodone, trazodone), antipsychotics (antipsychotic, haloperidol, olanzapine, clozapine, ziprasidone, aripiprazole, asenapine,

cariprazine, brexpiprazole, iloperidone, sertindole, risperidone, quetiapine, zotepine, lurasidone, chlorpromazine, perphenazine, amisulpride, sulpiride, butyrophenone, phenothiazine, pimozide, fluphenazine, perazine, promethazine, prochlorperazine, trifluoperazine, clopenthixol, thiothixene, zuclopenthixol, loxapine, perospirone, blonanserin) and mood stabilizers (mood stabilizer, lithium, valproic, valproate, lamotrigine, carbamazepine, oxcarbamazepine). The search resulted in 176 hits. We included studies published in English with a case-control design, specified to assess the risk of psychotropic medication and using as cases patients with first cataract diagnosis and/or surgery. Four studies were identified, one of them a conference abstract [6] and three additional were added from external sources.

## Antidepressant drugs

The first large case-control study, which assessed the association of antidepressants and cataract, included residents 65+ years with previously coronary revascularization in Canada [7]. The study included 18784 cases (73+/-8.1 years, 59.3% males) with first cataract diagnosis and 187840 age-matched controls. The association of cataract with antidepressant use was adjusted to gender, blood pressure and concomitant drugs. Current use of SSRI within 30 days from cataract diagnosis was associated with cataract (adjusted rate ratio: 1.15; 95% CI: 1.08-1.23). Regarding individual drugs, an association was observed with current use of fluvoxamine (adjusted rate ratio: 1.39; 95% CI: 1.07-1.8) and venlafaxine (adjusted rate ratio: 1.33; 95% CI: 1.14-1.5), but not current use of citalopram, fluoxetine, paroxetine and sertraline. Past use of antidepressants in general was not associated with cataract, but an association of past use of sertraline was observed (adjusted rate ratio: 1.19; 95% CI: 1.01-1.41). A secondary analysis assessed the risk for cataract surgery, and an association of current use of fluvoxamine and venlafaxine, as well as paroxetine (adjusted rate ratio: 1.23; 95% CI: 1.05-1.45) was observed. SSRI treatment needed 656 and 690 days on average from time of onset in order to associate with diagnosis and surgery of cataract, respectively.

Another case-control study with residents 50+ years of the Rochester Epidemiology Project (Minnesota, USA) found an association of antidepressant use and first-eye cataract surgery [8]. The study included 6024 cases, i.e. patients with first-eye cataract surgery and equal number of controls. There was no difference between cases (79+/-9 years, 40% males) and controls in terms of age and gender. Continuous prescription of SSRI for 1 or more year was associated with cataract surgery (crude odds ratio: 1.36, 95% CI: 1.23-1.51). The association remained even after adjusting for gender, diabetes and use of oral glucocorticosteroids. Regarding individual SSRI, citalopram (crude odds ratio: 1.53; 95% CI: 1.33-1.77) and sertraline (crude odds ratio: 1.27; 95% CI: 1.06-1.52) were associated with cataract-surgery, in contrast to paroxetine, fluoxetine, escitalopram and fluvoxamine. Prescription of SNRI for 1 or more year was also associated with cataract-surgery (crude odds ratio: 1.37; 95% CI: 1.11-1.7), with venlafaxine (crude odds ratio: 1.32; 95% CI: 1.05-1.67) and duloxetine (crude odds ratio: 1.82; 95% CI: 1.08-3.07). This association remained after adjusted for diabetes and corticosteroid use, but only in women.

A case-control study on the database of the National Health Insurance of Taiwan has also detected an association of antidepressant use and first cataract diagnosis [9]. The study included 7651 patients with schizophrenia or mood disorders and first cataract diagnosis and 6637 patients without cataract as controls. Age and gender was similar between cases (55.7 +/- 10.5 years, 35.8% males) and controls. The risk was adjusted to ophthalmic and other physical comorbidities, healthcare utilization, as well as use of antipsychotics or systemic steroids. An association with cataract diagnosis was observed for continuous use of SSRI (adjusted odds ratio: 1.26; 95% CI: 1.12-1.41), SNRI (adjusted odds ratio: 1.21; 95% CI: 1.02-1.43) and other antidepressants (adjusted odds ratio: 1.18, 95% CI: 1.18-1.34), i.e. bupropion, mirtazapine, trazodone and moclobemide. This association could be mediated by antidepressants with intermediate SERT affinity, i.e. dissociation constant 1-10 nM, (adjusted odds ratio: 1.68; 95% CI: 1.10-2.56) or use of multiple drugs with different SERT affinities (adjusted odds ratio: 1.31; 95% CI: 1.21-1.42). Re-

garding individual drugs, continuous use of venlafaxine (adjusted odds ratio: 1.44; 95% CI: 1.19-1.74), fluoxetine (adjusted odds ratio: 1.21; 95% CI: 1.01-1.46) and fluvoxamine (adjusted odds ratio: 1.47; 95% CI: 1.01-2.12) were associated with cataract, but not duloxetine, milnacipran, paroxetine, citalopram, sertraline or their combination with other antidepressants. An association with cataract was also observed for past use, i.e. >30 days from cataract diagnosis, of SSRI, TCA (adjusted odds ratio: 1.26; 95% CI: 1.16-1.36) and other antidepressants. The cumulative dosage of antidepressants required for cataract diagnosis seems to vary. Low cumulative dosage of paroxetine, citalopram, escitalopram and sertraline, as well as high cumulative dosage of venlafaxine, sertraline and fluvoxamine might be associated with cataract.

However, a recent case-control study on the UK-based Clinical Practice Research Datalink is inconsistent to previous studies [6]. The 206931 cases were patients 40+ years with first time cataract diagnosis and equal number of age and gender matched controls were included. Long term continuous prescription of SSRI was not associated with cataract diagnosis (adjusted odds ratio: 0.99; 95% CI: 0.94-1.03) in general, but it was associated in younger patients aged from 40 to 64 years (adjusted odds ratio: 1.24; 95% CI: 1.15-1.34). The risk was adjusted to body mass index, glucocorticosteroid use, hypertension, diabetes and smoking.

The recent case-control studies have examined the association of antidepressants with cataract diagnosis or surgery. The studies have adjusted the risk for several confounding factors, such as ophthalmic comorbidities, components of metabolic syndrome and concomitant cataractogenic drug use. However, only one study adjusted for body mass index and smoking [6], and it was unable to detect an association in general. In accordance to the recent studies, the Beaver Dam Study assessed the incidence of drug-associated cataract within 5 years of follow-up, and amitriptyline was associated with an odds ratio of 2.03 (95% CI 1.09-1.39) [10]. In addition preclinical evidence suggested possible roles of serotonin, catecholamines and their receptors on the development of cataract [7].

Case-control studies cannot confirm a causal relationship, as well as several confounding factors could be encrypted, such as family history of cataract. Populations at risk could be younger patients on long term continuous use of antidepressants. In addition, differences among individual antidepressants could emerge and intermediate SERT affinity, along with NET inhibition could be possible mediators. Longitudinal prospective studies should further establish the association between antidepressant and cataract, but ocular examination of antidepressant users, especially younger patients with comorbidities, could be justified.

### Antipsychotic drugs

The first case-control study assessed the risk of antipsychotics for cataract surgery using the British Columbia Ministry of Health Database [11]. The study included 162501 cases of cataract surgery and 650004 controls. The age and gender of cases (74.4 +/-11.8 years, 41.6% males) were similar to controls. The risk was adjusted to age, gender, concomitant SSRI, antidiabetics and steroids, as well as history of uveitis, vitrectomy and hypertension. Prescription of atypical antipsychotics within 90 days of cataract surgery was protective (adjusted rate ratio: 0.84; 95% CI: 0.8-0.89). In addition, current use of typical antipsychotics was also protective (adjusted rate ratio: 0.84; 95% CI: 0.74-0.96), though haloperidol has suggested to be the most common prescribed antipsychotic. A dose-response of protection was observed, with higher number of prescriptions (more than 7 within the previous year) were associated with lower rate ratio (adjusted rate ratio: 0.7; 95% CI: 0.65-0.75), in comparison to smaller number of prescriptions (adjusted rate ratio: 0.85; 95% CI: 0.79-0.91).

Two studies on the National Health Insurance of Taiwan examined the role of antipsychotics on cataract development. The first one included 2222 patients with schizophrenia and cataract diagnosis were defined as cases and 2144 patients with schizophrenia without cataract diagnosis as controls [12]. There was no difference in age and gender between cas-

es (53.1+/- 11.3 years, 39% males) and controls. The risk was adjusted to ophthalmic and other physical comorbidities, antidepressant or steroid use, as well as utilization of the health-care system. An association with cataract was not observed for continuous use of atypical (adjusted odds ratio: 1.1; 95% CI: 0.94-1.3) and typical antipsychotics (adjusted odds ratio: 1.08; 95% CI: 0.91-1.29), when compared to past use of antipsychotics, i.e. > 90 days before of the cataract diagnosis. Regarding individual atypical antipsychotics, none was associated with cataract. In contrast to the previous case-control study [11], a protective association, i.e. the higher boundary of odds ratio < 1, was not observed.

However, a protective association was observed in the second study using patients with bipolar disorder [2]. The cases were 1684 patients with bipolar disorder and cataract diagnosis (55.3+/-10.3 year, 36% females) and 1608 matched controls with bipolar disorder and without a cataract diagnosis. Similar to the previous study, the risk was adjusted to ophthalmic and other physical comorbidities, utilization of the health system, as well as use of steroids, antidepressants and mood stabilizers. Continuous or past use of atypical antipsychotics seem to be protective (adjusted odds ratio: 0.71; 95% CI: 0.59-0.85), whereas an association with typical antipsychotics was not observed (adjusted odds ratio: 0.97; 95% CI: 0.71-1.34). In addition, continuous or past use of individual atypical antipsychotic was not associated with cataract.

Several lines of evidence suggest the risk of typical antipsychotics, especially phenothiazines, for cataract, but the risk of atypical antipsychotics is still under question [13]. Earlier studies suggest that patients with schizophrenia have a lower risk for cataract in general, but a higher prevalence of anterior subcapsular cataract [14]. Phenothiazines seem to induce lenticular pigmentation and the associated anterior subcapsular cataract [13]. Case reports suggest that chlorpromazine-induced lenticular opacities could cause visual impairment, which could be reversed after switching to risperidone [15]. Regarding the newer antipsychotics, high doses of quetiapine has been accused for cataract in

preclinical research, so that biannual ocular examination has been suggested. Though, clinical evidence was not able to replicate these results in humans. A recent 2-year randomized open label study suggested that quetiapine was not cataractogenic in comparison to risperidone [16]. However, bilateral cataract has been reported in a 27-year old male with bipolar disorder on treatment with risperidone and lithium [17].

The above case-control studies suggest a possible protective mechanism of atypical antipsychotics against cataract development. It is suggested that antagonism of serotonin receptors, as well as anti-oxidative and anti-inflammatory properties could play important roles [2]. Individual typical antipsychotics were not tested. However, haloperidol could be the most frequently prescribed typical antipsychotic, underestimating the risk [11]. Important confounding factors such as smoking, family history of cataract, obesity was also not included in these studies. The possible protective association should also be replicated in other ethnicities and prospective studies.

## Mood stabilizers

A secondary analysis of the case-control study on the National Health Insurance Research Database of Taiwan [9], has studied the association between mood stabilizers and cataract diagnosis in patients with schizophrenia or mood disorders [5]. The study included 7651 patients with schizophrenia or mood disorders and first cataract diagnosis and 6637 patients without cataract as controls. The risk was adjusted to comorbidities, concomitant cataractogenic drugs and healthcare utilization. Use of mood stabilizers for more than 2 years was associated with cataract (adjusted odds ratio: 1.14; 95% CI: 1.01-1.29), and the risk remained only for doses higher than the half of the daily defined dose (adjusted odds ratio: 1.28; 95% CI: 1.08-1.53). Regarding individual drugs, long-term use of lithium alone (adjusted odds ratio: 1.39; 95% CI: 1.01-1.92) or combined with other mood stabilizers (adjusted odds ratio: 1.44; 95% CI: 1.13-1.85), as well as valproic acid combined with other mood stabilizers (adjusted odds ratio: 1.26; 95% CI: 1.02-1.57), but not

alone, was associated with cataract. Association was not observed with long term use of carbamazepine, lamotrigine and their combinations with other mood stabilizers. However, their sample size was small and probably not sufficient.

The role of mood stabilizers on the risk of cataract is studied to a lesser degree than antidepressants and antipsychotics. Carbamazepine, lamotrigine and valproic acid are also used as anticonvulsants. A study has suggested that patients with epilepsy on carbamazepine (odds ratio: 1.4, 95% CI: 1.05–1.8) may have been in higher risk for cataract surgery, in contrast to barbiturates and valproic acid [18]. In addition, a case report of carbamazepine-induced bilateral cataract in a 14-year old boy have been reported [19]. The cataractogenic properties of mood stabilizers could lie on inhibiting anti-oxidant mechanisms or inducing other ocular side effects [5].

## Conclusion

Psychotropic medication could alter ocular physiology contributing to cataract development. Use of antidepressant drugs seem to predispose to cataract, especially long-term use and probably in younger patients. However, there is discrepancy regarding the risk of individual drugs, but dual mechanism and intermediate SERT affinity has been suggested as possible risk factors. Furthermore, mood stabilizers could also associate with cataract, despite the inconsistent results on individual drugs. On the other hand, atypical antipsychotics and high potency typical antipsychotics seem not to associate with cataract. Atypical antipsychotic drugs might also be protective against cataract, despite sparse preclinical and clinical evidence of their harmful effects. Phenothiazines and low-potency typical antipsychotics could induce lenticular opacities and cataract. A harmful or protective causal relationship between psychotropic medication and development of cataract cannot be established by case-control studies, and further research is needed. However, ocular examinations should be suggested to patients on psychotropic medication, especially on antidepressant or mood stabilizers, as well as with comorbidities and concomitant use of cataractogenic drugs.



## References

1. Prokofyeva, E., A. Wegener, and E. Zrenner, Cataract prevalence and prevention in Europe: a literature review. *Acta Ophthalmol* 2013, 91(5): p. 395-405. PMID: 22715900 , DOI: 10.1111/j.1755-3768.2012.02444.x
2. Chu, C.S., et al., Association between antipsychotic drug use and cataracts in patients with bipolar disorder: A population-based, nested case-control study. *J Affect Disord* 2017, 209: 86-92. PMID: 27889598 , DOI: 10.1016/j.jad.2016.11.019
3. Carvalho, A.F., et al., The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. *Psychotherapy and Psychosomatics* 2016, 85(5): 270-288. PMID: 27508501, DOI: 10.1159/000447034
4. Shahzad, S., et al., Cataract occurrence with antipsychotic drugs. *Psychosomatics* 2002, 43(5): 354-9. PMID: 12297603 , DOI: 10.1176/appi.psy.43.5.354
5. Chu, C.-S., et al., Associations between use of mood stabilizers and risk of cataract: A population-based nested case-control study. *J Affective Disorders* 2017, 227 (Supplement C): p. 79-81. PMID: 27889598 , DOI: 10.1016/j.jad.2016.11.019
6. Becker, C., S.S. Jick, and C.R. Meier, Selective Serotonin Reuptake Inhibitors and Cataract Risk: A Case-Control Analysis. *Ophthalmology* 2017, 124(11): 1635-1639, doi: 10.1016/j.ophtha.2017.05.002
7. Etminan, M., F.S. Mikelberg, and J.M. Brophy, Selective serotonin reuptake inhibitors and the risk of cataracts: a nested case-control study. *Ophthalmology* 2010, 117(6): 1251-5, doi: 10.1016/j.ophtha.2009.11.042
8. Erie, J.C., et al., Selective serotonin reuptake inhibitor use and increased risk of cataract surgery: a population-based, case-control study. *Am J Ophthalmol* 2014, 158(1): 192-197.e1. MID: 24631758, PMCID: PMC4356987, DOI: 10.1016/j.ajo.2014.03.006
9. Chou, P.H., et al., Antidepressants and risk of cataract development: A population-based, nested case-control study. *J Affect Disord* 2017, 215: 237-244. PMID: 28342338 , DOI: 10.1016/j.jad.2017.03.044
10. Klein, B.E., et al., Drug use and five-year incidence of age-related cataracts: The Beaver Dam Eye Study. *Ophthalmology* 2001, 108(9): 1670-4. PMID: 11535471
11. Pakzad-Vaezi, K.L., M. Etminan, and F.S. Mikelberg, The association between cataract surgery and atypical antipsychotic use: a nested case-control study. *Am J Ophthalmol* 2013, 156(6): 1141-1146. doi: 10.1016/j.ajo.2013.07.012
12. Chou, P.H., et al., Use of atypical antipsychotics and risks of cataract development in patients with schizophrenia: A population-based, nested case-control study. *Schizophr Res* 2016, 174(1-3): 137-43. PMID: 27061658 , DOI: 10.1016/j.schres.2016.03.027
13. Souza, V.B., et al., Cataract occurrence in patients treated with antipsychotic drugs. *Rev Bras Psiquiatr* 2008, 30(3): 222-6. PMID: 18833422
14. McCarty, C.A., et al., Schizophrenia, psychotropic medication, and cataract. *Ophthalmology*, 1999, 106(4): 683-7. PMID: 10201587 , DOI: 10.1016/S0161-6420(99)90151-3
15. Gowda, G.S., et al., Kerato-lenticular ocular deposits and visual impairment with prolonged chlorpromazine use: A case series. *Asian J Psychiatry* 2017, 25: 188-190. PMID: 28262147 , DOI: 10.1016/j.ajp.2016.11.002
16. Laties, A.M., Flach AJ, Baldycheva I, Rak I, Earley W, Pathak S., Cataractogenic potential of quetiapine versus risperidone in the long-term treatment of patients with schizophrenia or schizoaffective disorder: a randomized, open-label, ophthalmologist-masked, flexible-dose, non-inferiority trial. *J Psychopharmacol* 2015, 29(1): 69-79. PMID: 25315830 , DOI: 10.1177/0269881114553253
17. Patel, E. and J.A. Gallego, Bilateral cataracts in a young patient with bipolar disorder on treatment with risperidone. *Aust N Z J Psychiatry* 2016, 50(12): 1210, DOI: 10.1177/0004867416655604
18. Hanhart J, Vinker S, Nemet A, Levartovsky S, Kaiserman I., Prevalence of Epilepsy among Cataract Patients. *Curr Eye Res* 2010, 35(6): 487-91. PMID: 20465442 , DOI: 10.3109/02713681003664915
19. Kinoshita A, Kitaoka T, Oba K, Amemiya T., Bilateral drug-induced cataract in a patient receiving anticonvulsant therapy. *Jpn J Ophthalmol* 2004, 48(1): 81-2, DOI: 10.1007/s10384-003-0017-z