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# Amiodarone-Associated Optic Neuropathy: A Critical Review

**Rod S. Passman, MD MSCE**[1], **Charles L. Bennett, MD PhD MPP**[2], **Joseph M. Purpura, MD MS**[3], **Rashmi Kapur, MD**[4], **Lenworth N. Johnson, MD**[5], **Dennis W. Raisch, RPh, MS PhD**[6], **Dennis P. West, PhD**[7,8], **Beatrice J. Edwards, MD MPH**[9], **Steven M. Belknap, MD**[7,10], **Dustin B. Liebling, BA**[9], **Mathew J. Fisher, BA**[9], **Athena T. Samaras, BA**[7], **Lisa-Gaye A. Jones, BS**[11], **Katrina-Marie E. Tulas, BS**[9], and **June M. McKoy, MD MPH JD MBA**[8,9]

[1]Division of Cardiology Northwestern University Feinberg School of Medicine, Chicago, IL

[2]South Carolina Center of Economic Excellence for Medication Safety and Efficacy and the Southern Network on Adverse Reactions (SONAR), South Carolina College of Pharmacy, the University of South Carolina, Columbia, SC

[3]Department of Obstetrics and Gynecology Northwestern University Feinberg School of Medicine Chicago, IL

[4]Department of Ophthalmology and Visual Sciences, University of Illinois, College of Medicine, Chicago, IL

[5]Departments of Ophthalmology and Neurology and the Mason Eye Institute University of Missouri-Columbia School of Medicine, Columbia, MO

[6]VA Cooperative Studies Program, Clinical Research Pharmacy Coordinating Center and College of Pharmacy, Albuquerque, NM.

[7]Department of Dermatology Northwestern University Feinberg School of Medicine Chicago, IL

[8]Robert H. Lurie Comprehensive Cancer Center Northwestern University Feinberg School of Medicine, Chicago, IL

[9]Division of Geriatric Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

[10]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

[11]University of Iowa, Iowa City, IA.

## Abstract

Although amiodarone is the most commonly prescribed antiarrhythmic drug, its use is limited by serious toxicities, including optic neuropathy. Current reports of amiodarone associated optic neuropathy identified from the Food and Drug Administration's Adverse Event Reporting System (FDA-AERS) and published case reports were reviewed. A total of 296 reports were identified: 214 from AERS, 59 from published case reports, and 23 from adverse events reports for patients



Corresponding Author: June M. McKoy, MD MPH JD MBA Department of Medicine Northwestern University Feinberg School of Medicine 645 N. Michigan Avenue, Suite 630 Chicago, IL. 60611 Fax: 312-695-3331 / Phone: 312-695-5287 j-mckoy@northwestern.edu.



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enrolled in clinical trials. Mean duration of amiodarone therapy before vision loss was 9 months (range 1-84 months). Insidious onset of amiodarone associated optic neuropathy (44%) was the most common presentation, and nearly one-third were asymptomatic. Optic disc edema was present in 85% of cases. Following drug cessation, 58% had improved visual acuity, 21% were unchanged, and 21% had further decreased visual acuity. Legal blindness (< 20/200) was noted in at least one eye in 20% of cases. Close ophthalmologic surveillance of patients during the tenure of amiodarone administration is warranted.

**Keywords**

amiodarone; vision loss; optic neuropathy

## INTRODUCTION

Amiodarone emerged as the most commonly prescribed antiarrhythmic drug in North America in the 1970s.[1] In 2000, more than 400,000 individuals received amiodarone for the treatment of atrial fibrillation alone, an increase of over 200% compared to 1997 and a 32-fold increase since 1991.[2] Studies have shown amiodarone to be superior to other antiarrhythmic agents for the treatment of atrial fibrillation, including sotalol and propafenone.[3, 4]

Amiodarone's clinical efficacy has been tempered by its toxicity with almost fifty percent of long-term users resultantly discontinuing the drug. [5-8] Furthermore, amiodarone toxicity is ubiquitous, affecting the lungs, thyroid, skin, nervous system liver, and eyes.[8] These toxic effects are sometimes a function of the cumulative dose administered, but can occur shortly after drug initiation.[9, 10] Therapeutic drug monitoring of blood concentrations of amiodarone and its metabolite, N-desethylamiodarone, may reduce the risk of amiodarone toxicity, but limited evidence supports this claim.[11,12]

In 2004, the Food and Drug Administration (FDA) issued a Boxed warning in amiodarone's package insert. This warning was not driven by ocular toxicities, though more than 90% of amiodarone users develop corneal micro-deposits, with <5% reporting related halo vision, and almost 2% of users develop visual loss from amiodarone induced optic neuropathy, and some exposed patients have suffered permanent blindness; [8, 9, 13, 14, 15] Rather, the warning was because of potentially fatal toxicities related to amiodarone-associated hypersensitivity pneumonitis and interstitial/alveolar pneumonitis. Subsequent mailed “Dear patients” letters, which have been shown to escape delivery to patients in over 40% of prescriptions filled, therefore made no mention of ocular concerns.[16,17, 18]

Clinical findings of amiodarone-associated optic neuropathy share features of nonarteritic anterior ischemic optic neuropathy, the most common cause of visual loss from optic nerve disease among individuals over age 50 years.[19-21] These conditions, however, differ with respect to gender-distribution, laterality, optic disc appearance on funduscopic examination, and duration of disc edema. Amiodarone associated optic neuropathy more often occurs in men, while nonarteritic anterior ischemic optic neuropathy has equal sex predilection. Both are associated with vision loss and optic disc edema. Vision loss in nonarteritic anterior ischemic optic neuropathy is often acute in onset, while in amiodarone associated optic neuropathy tends to be insidious in onset. Nonarteritic anterior ischemic optic neuropathy is usually unilateral, whereas two-thirds of amiodarone associated optic neuropathy cases present bilaterally with simultaneous optic neuropathy.[9, 13] Additionally, whereas optic disc edema in nonarteritic anterior ischemic optic neuropathy generally resolves within weeks, median duration of optic disc edema in amiodarone associated optic neuropathy is 3 months.

Finally, whereas nonarteritic anterior ischemic optic neuropathy occurs most often in patients with small optic nerve cup-disc ratio there is no particular cup-disc ratio associated with amiodarone associated optic neuropathy.[9, 19, 22, 23]

Herein, investigators from the Research on Adverse Drug Events And Reports (RADAR), an independent pharmacosurveillance program focusing on identification, evaluation, and dissemination of information describing serious adverse drug reactions (sADRs),[2425] provide a critical review of the largest number of cases of amiodarone-associated optic neuropathy.

## METHODS

Institutional Review Board (IRB) approval was obtained from Northwestern University prior to study commencement. Reports of amiodarone associated optic neuropathy were identified from FDA-AERS (January, 1993 and May, 2011) and published cases through May, 2011. Medline (PubMed and EMBASE) search terms included optic neuropathy, pseudotumor, optic neuritis, vision loss, and amiodarone. Ovid and Cochrane Collaboration MeSH terms included Amiodarone/ ae (adverse effects), Amiodarone/pd (pharmacology), Eye/ bs (blood supply), Eye/ de (drug effects), Optic Neuropathy, ischemic/ ci (chemically induced) and Optic Neuropathy, ischemic/ dt (drug therapy). Foreign language articles were translated by physicians fluent in the respective languages (R.K.). Other data sources included the FDA-approved package inserts and notices to providers and patients. Abstracted data elements included patient demographics, clinical findings, concomitant drug use, and dose and duration of amiodarone therapy. Clinical findings related to optic neuropathy identified after initiation of amiodarone included optic disc edema, visual field defects, optic disc atrophy, optic disc hemorrhages, afferent pupillary defect, and change in visual acuity/subjective blurring of vision. Criteria for diagnosing optic neuropathy, the association with amiodarone, and the level of diagnostic certainty were defined and assessed from data elements provided from each report (Table I). Permanent (legal) blindness rates in at least one eye of each patient with diagnosed amiodarone associated optic neuropathy were calculated using the United States Public Health Services (USPHS) definition of visual acuity of 20/200 or worse.[26]

The AERS data comprised all MedWatch cases reported to the FDA between January, 1993 and October, 2010. The AERS was searched for all cases of optic neuropathy using all relevant preferred terms from the Medical Dictionary for Regulatory Affairs (MedDRA) terminology and all synonyms for amiodarone and data were summarized for relevant cases. Additionally, data mining signal detection ratios were calculated to estimate signal strength associated with optic neuritis among patients receiving amiodarone. We calculated the proportional reporting ratio (PRR)[27] and the empirical Bayesian geometric mean (EBGM),[28, 29] two ratios commonly applied to voluntary adverse event reporting data.

Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as percent of total. Normally distributed continuous variables were compared using t-tests while variables with non-normal distributions were compared using non-parametric statistics. Categorical variables, including completeness of data, were compared using Chi-square tests and, where appropriate, Fisher's exact test. A $p \leq 0.05$ was considered statistically significant.

## RESULTS

A total of 296 cases of amiodarone associated optic neuropathy were identified: 214 from AERS, 59 from published case reports, and 23 from adverse events reports for patients

enrolled in clinical trials. Due to the potential for case reports duplication in AERS, we reviewed the literature cases and those reported to AERs separately. In the literature reports, mean patient age was 66 ± 11 years with 74% male. Mean duration of amiodarone use was 33± 48 months while median duration of therapy was 9 months. The median dose of amiodarone used in these reports was 200 mgs (range 57 – 1200 mg/day). Indication for amiodarone use among cases reported in AERS was atrial fibrillation (50%); other atrial and ventricular arrhythmias (50%); ventricular arrhythmias accounted for over 90% of indications for amiodarone use in published cases. Eighty patients from the published literature were characterized as having definitive findings of optic neuropathy; [9, 13, 14, 30-56] mean age of these patients was 63 ± 10 years (range 32-87 years) and 67 (84%) of these patients were male.

Data summarization from FDA reports was more difficult due to incompleteness in both the reports from the health professionals and pharmaceutical suppliers. (Table 2) From information reported, the average age was 68 ± 11 years (range 30-94) with 144 (71%) being male. Mean duration of amiodarone therapy (reported in n= 80 cases) before manifestation of visual symptoms was 9 months (range 1-84 months), while median duration of therapy was 6 months.

The most common clinical presentation was insidious onset of optic neuropathy (44%). Other presentations included acute onset of optic neuropathy (21%), retrobulbar optic neuropathy (29%), pseudotumor cerebri/elevated intracranial pressure (8%), and delayed-progressive onset (6%). In some instances, ocular symptoms varied between eyes in the same patient. Nearly one-third of the patients were asymptomatic. Patients presenting with ocular symptoms reported either acute (19%) or insidious (26%) monocular vision loss, or acute bilateral (10%) or insidious (14%) visual loss. The signal detection ratios for optic neuritis and blindness were strong ($p<0.001$). The PRR, representing the relative number of reports of optic neuropathy for amiodarone as compared to those for all drugs, was 4.62 (95% confidence interval (CI): 4.01-5.34) and the EGBM, which adjusts for sampling variability, was 4.56 (95% CI: 3.38-4.99); only 1 drug with more than 150 cases of optic neuritis/blindness in AERS had stronger signal detection ratios.

Detailed eye examination findings were included in adverse event reports from the published literature, but not from the MedWatch database. Among 80 published adverse event reports, 69% identified optic disc edema in at least one eye. Of note, bilateral optic disc edema was observed in 12% of asymptomatic patients, 64% of patients who presented with monocular visual loss, and 68% of patients reporting bilateral visual loss. Visual acuity at presentation ranged from 20/15 to recognizing only light. In the published literature, 61 of the 80 cases provided information on amiodarone's discontinuation at the onset of clinical findings. Of these 61, 77% discontinued the drug. More than half (58%) of the patients who discontinued amiodarone improved in visual acuity whereas only 21% maintained the same vision; 21% experienced decreased visual acuity. Permanent (legal) blindness was noted in at least one eye in 21% of the case reports.

Concurrent drug therapy reporting, which was also evaluated to identify other risk factors for amiodarone associated optic neuropathy, was in many cases incomplete. However, when reported, digitalis was the most frequent concurrent drug. For patients on concurrent therapy with digitalis, only a few were identified as having a drug interaction.

Published case reports provided detailed information on funduscopic findings, time course, and clinical outcomes;[9] the most common reported presentation was insidious onset, which on funduscopy generally revealed bilateral optic disc edema, although most patients reported vision loss in only one eye. A second presentation was that of acute unilateral or bilateral

vision loss, with funduscopic findings similar to those seen with nonarteritic anterior ischemic optic neuropathy. The third form was consistent with retrobulbar optic neuropathy. Vision loss was either acute or insidious and one or both eyes were affected. These patients are the most difficult to identify as additional tests to rule out intra-cerebral mass lesions and other etiologies that cause vision loss in the presence of normal optic nerves are required. The fourth form was that of increased intracranial pressure presenting either acutely or insidiously. The final form was delayed progressive optic neuropathy. Patients may present with visual symptoms prior to the development of optic disc edema and, because amiodarone's half-life is 35 to 110 days, edema may even develop after amiodarone is discontinued.[57] In one cohort, visual acuity at presentation ranged from 20/15 to light perception. Median visual acuity was 20/30, and 32 (58%) patients had 20/40 or better visual acuity. Ten (18%) patients suffered legal blindness, with visual acuity of 20/200 or worse on initial presentation, contributing to the risk benefit calculation when contemplating amiodarone use.

## DISCUSSION

Clinically, amiodarone associated optic neuropathy has been characterized by insidious onset, protracted disc swelling leading to bilateral visual loss, and visual findings that require several months to stabilize after the drug's discontinuation.[13] Our review and the 2004 report from Johnson, et al.[9] indicate that clinical presentations of amiodarone associated optic neuropathy can be acute in onset and unilateral, and not necessarily insidious in onset and bilateral.[9] However, most initial unilateral cases subsequently developed involvement in the fellow eye as expected with systemic toxicity.

A prospective, controlled, double-blind study by Mindel et al, of over 1600 subjects followed for a median 45.5 months, failed to show an association between amiodarone and bilateral toxic vision loss.[58] However, patients in this study did not undergo prospective ophthalmologic evaluations. Mindel et al based their conclusion on post-hoc analysis of interval reports where a “yes” was entered by the nurse coordinator to the query “Optic Neuritis.” Because the median visual acuity loss in previously reported cases of amiodarone-associated optic neuropathy is 20/30, patients in the study by Mindel et al. with unilateral or mild bilateral visual loss would go undetected. [9,58]

Ultra-structural findings of the optic nerve in patients with amiodarone-associated optic neuropathy are similar to those seen in patients with amiodarone-induced peripheral neuropathy. Mansour et al. identified multiple lamellated inclusion bodies in large axons of the optic nerve, while demyelination or loss of large axons was not seen.[59] Demyelination, loss of large axons, and lamellated bodies are seen in the axoplasm and schwann cells of peripheral nerves in amiodarone-associated peripheral neuropathy.[60, 61] Accumulation of lamellated bodies has been attributed to inhibition of lysosomal sphingomyelinases.[59, 62] It is not known if histopathologic differences are due to myelination by oligodendrocytes of central nerves or differences in the time course of ocular versus peripheral neuropathy findings before clinical symptoms develop.

While this report describes a large series with presumed amiodarone associated optic neuropathy, a direct causal link between amiodarone use and optic neuropathy remains speculative. Patients requiring amiodarone therapy frequently have risk factors similar to those with nonarteritic anterior ischemic optic neuropathy , including sleep apnea, older age, diabetes mellitus, and hypertension.[9] Although all patients on amiodarone have cardiac arrhythmias, to our knowledge, no study has shown that cardiac arrhythmia independently poses a risk for nonarteritic anterior ischemic optic neuropathy.

Concurrent drug therapy can be an important contributing factor to the development of the toxic optic neuropathy of amiodarone associated optic neuropathy. However, from our review not all patients with amiodarone associated optic neuropathy used concomitant drugs. Among the cases included in this study, digoxin was the most frequently reported co-administered drug. Amiodarone causes a dose-dependent increase in digoxin levels, possibly due to inhibition of digoxin secretion from renal tubules and inhibition of the P-glycoprotein mediated digoxin transporter system.[63] Of note, digoxin and amiodarone can similarly decrease vision and alter color perception, presumably as a result of optic nerve damage.[64, 65] In some of the reported cases, the addition of amiodarone may have exacerbated the findings of digoxin-induced optic neuropathy. Therefore digoxin dose should be empirically decreased by half and serum level closely monitored when co-administered with amiodarone. Early referral to an ophthalmologist is recommended for evaluation of visual acuity, color vision, automated perimetry, and dilated funduscopic examination for signs of early (asymptomatic) optic neuropathy - disc edema and abnormal visual fields.

Amiodarone ocular toxicity generally occurs within 1 year of drug initiation, with median time to onset of visual symptoms within 6 months. While the outcome of this toxicity is variable, permanent blindness in at least one eye has been reported for one-fifth of affected individuals. As noted in our results, the risk of nonarteritic anterior ischemic optic neuropathy (PRR 4.62) is higher for amiodarone compared with several other drugs, including ethambutol, which has long been “accepted” by neuro-ophthalmologists as a cause of optic neuropathy with an incidence of <1%,[66, 67] although no properly designed evidence-based study has been performed to show true cause-effect. Therefore, though persons taking amiodarone may be vasculopaths by definition, this does not diminish the drug's toxicity in this domain. Our review supports modification of the “Boxed” warning and “Dear Patient” documents to specifically include amiodarone associated optic neuropathy as a significant adverse event so that prescriber and patient vigilance is elevated. The manufacturers of amiodarone recommend routine ophthalmologic screening for all patients, but give no specific time points for follow-up assessments. The Heart Rhythm Society recommends ophthalmologic evaluation at baseline for patients with preexisting visual impairment or during follow-up if visual symptoms develop. The National Institute for Health and Clinical Excellence (NICE) guidelines for atrial fibrillation recommend amiodarone use, but are silent on recommendations relative to monitoring side-effects.[68] Because most cases of amiodarone-associated optic neuropathy occur within 12 months of drug initiation, Johnson and colleagues suggested equally spaced interval evaluations within the first year, followed by annual examinations.[9, 13]

Finally, when ocular toxicity is suspected physicians should report ophthalmologic findings, concomitant drugs, drug dose and duration of amiodarone therapy, and follow-up findings to the FDA's MedWatch program. Additionally, they should alert patients taking amiodarone of the need for baseline and regular follow-up ophthalmologic screening.

A limitation of this study is the incompleteness of the case reporting to the FDA's AERS (Table 2). Of 214 FDA reports, none from either health care professionals or pharmaceutical suppliers was complete; only 15/214 was “partially complete.” Improvement in completeness of reporting of amiodarone ocular toxicity could strengthen the call for a Boxed warning for this sADR. Another study limitation relates to the PRR and EBGM, which stems from the voluntary nature of adverse drug reaction reporting to the FDA. Fewer than 10% of ADRs are reported to MedWatch. Therefore, external factors, such as publicity associated with a specific ADR, its seriousness, and the ability of the health professional to identify a drug/reaction relationship impact the likelihood of addition of the event to the system. Since PRR/EBGM represents an estimate of the comparative reporting rates for

specific reactions to individual drugs, these rates are subject to external factors. The PRR/EBGM is thus not used as definitive evidence of the reaction, but with supporting information signals the existence of a direct relationship between the drug and reaction.

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## Table 1

Criteria for completeness of reporting for possible Amiodarone associated optic neuropathy cases

| | **Data Elements** | **Scoring (based on number of elements reported)** |
|---|---|---|
| Optic Neuropathy Diagnosis **(1 point for each element)** | optic disc edema, visual field defect, color vision abnormalities, optic disc atrophy, optic disc hemorrhages, afferent pupillary defect, intracranial hypertension, and change in visual acuity/subjective blurring of vision | Complete (6-8)<br>Partially complete (3-5)<br>Incomplete (<3) |
| Association With Amiodarone **(1 point for each element)** | dose, duration of treatment, duration of treatment before presentation, other simultaneous drug therapy, outcome post-discontinuation, change in visual acuity after initiation of amiodarone | Complete (5-6)<br>Partially complete (3-4)<br>Incomplete (<3) |
| Diagnostic certainty | completeness of information provided and the diagnosis given by the reporting physician | Probable (patient was diagnosed with optic neuropathy/neuritis) Possible (patient had one or more features suggestive of optic neuropathy/ neuritis) Incomplete (no information is present on the final diagnosis or the presence or absence of features suggestive of optic neuropathy/neuritis) |

## Table 2

Completeness of cases reported to the FDA's Adverse Events Reporting System and of published reports (See Methods Section for definitions)

| | FDA Reports | | Published Reports | |
|---|---|---|---|---|
| | From health professionals | Pharmaceutical Suppliers Reports | Medline Case Reports | Medline Clinical Trials |
| | N=29 | N=185 | N=57 | N=23 |
| Optic Neuropathy Diagnosis | | | | |
| Complete | 0 | 0 | 15 (26%) | 1 (4%) |
| Partially Complete | 3 (10%) | 12 (6%) | 38 (67%) | 22 (96%) |
| Incomplete | 26 (90%) | 173 (94%) | 4 (7%) | 0 |
| Association with amiodarone | | | | |
| Complete | 0 | 0 | 17 (30%) | 15 (65%) |
| Partially Complete | 4 (14%) | 18 (10%) | 39 (68%) | 8 (35%) |
| Incomplete | 25 (86%) | 167 (90%) | 1 (2%) | 0 |
| Diagnostic Certainty | | | | |
| Probable | 11 (38%) | 53 (29%) | 57 (100%) | 9 (39%) |
| Possible | 1 (3%) | 12 (7%) | 0 | 14 (61%) |
| Incomplete | 17 (59%) | 120 (64%) | 0 | 0 |