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Nonadherence or Nonpersistence to Intravitreal Injection Therapy for Neovascular Age-Related Macular Degeneration

A Mixed-Methods Systematic Review

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Topic: Systematic review of risk factors for nonadherence and nonpersistence to intravitreal anti–vascular endothelial growth factor (VEGF) injection therapy for neovascular age-related macular degeneration (nAMD).

Clinical Relevance: Lack of adherence (nonadherence) or undertreatment (nonpersistence) with respect to evidence from clinical trials remains a significant barrier to optimizing real-world outcomes for patients with nAMD. Contributing factors and strategies to address this are poorly understood.

Methods: Studies that reported factors for nonadherence and nonpersistence to anti-VEGF therapy as well as studies examining strategies to improve this were included. Trial eligibility and data extraction were conducted according to Cochrane review methods. Risk of bias was assessed using the Mixed Method Assessment Tool and certainty of evidence evaluated according to the GRADE Confidence in the Evidence from Reviews of Qualitative Research tool. Data were collated descriptively.

Results: Of the 1284 abstract results screened, 124 articles were assessed in full and 37 studies met the inclusion criteria. Definitions of nonadherence and nonpersistence varied or were not reported. Nonpersistence occurred early, with up to 50% of patients stopping treatment by 24 months. High rates of nonadherence were similarly reported, occurring in 32% to 95% of patients. Certainty of this finding was downgraded to a moderate level because of the heterogeneity in definitions used across studies. Multiple factors determine nonadherence and nonpersistence, including at the condition, therapy, patient, social/economic, and health systems/healthcare team levels. Moderate quality evidence points to lower baseline vision and poorer response to treatment as condition-related variables. The effects of other factors were of lower certainty, predominantly due to small numbers and potential biases in retrospective assessment. Although many factors are not modifiable (e.g., patient comorbidity), other factors are potentially correctable (e.g., lack of transport or mismatched patient expectations). Evidence on strategies to improve adherence and persistence is limited, but where available, these have proven effective.

Conclusions: Awareness of factors related to poor patient adherence and persistence in nAMD could help identify at-risk populations and improve real-world outcomes. Further work is required to develop uniform definitions and establish high-quality evidence on interventions that can be easily implemented. *Ophthalmology 2021;128:234-247 © 2020 by the American Academy of Ophthalmology*

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Intravitreal anti–vascular endothelial growth factor (VEGF) injections have revolutionized the treatment of neovascular age-related macular degeneration (nAMD).[1,2] Landmark clinical trials have demonstrated that anti-VEGF injections stabilize disease, and initial and prolonged visual gains are common.[3,4]

Treatment of nAMD requires frequent intravitreal injections. Although the early pivotal trials used a monthly injection regimen, given the difficulties with such intensive treatment, other more flexible regimens have since been developed, with pro re nata (PRN) and treat-and-extend (T&E) protocols the most commonly used.[2]

Real-world evidence suggests that even with these "less taxing" alternate dosing regimens, outcomes seen in practice mostly do not reach the levels achieved in trial settings, with the discrepancy possibly due to lack of adherence to clinical trial regimens (defined in this article as nonadherence) or lack of persistence with following recommended clinical trial regimens over time (defined as nonpersistence). For example, a recent meta-analysis of real-world observational

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data based on approximately 26 000 patients reported a mean visual gain of only +5.0 Early Treatment of Diabetic Retinopathy Study letters after 12 months of treatment, with a mean number of 5.4 injections over 8.3 visits.[5] This is well below the +11.3 letters seen in the ANCHOR trial with monthly intravitreal ranibizumab[6] and +8.9 letters in VIEW1/VIEW 2 studies[7] with intravitreal aflibercept every 8 weeks. Long-term results from both clinical trials and registry data also confirm this finding, with more frequent injections consistently showing better visual outcomes.[8,9]

Given the importance of encouraging ongoing and frequent injections, there is a relative lack of awareness among physicians and the health community of the barriers that lead to the inter-related phenomenon of nonadherence and nonpersistence of anti-VEGF treatment in nAMD in the real world. Terminology and agreed definitions may not exist. There is even less discussion on strategies to correct or counteract these barriers. Previous studies have attempted to look at this from a local practice level or focused only on the patient experience.[10,11] However, a comprehensive analysis has not been performed to date. The purpose of this systematic review is to assess the factors affecting treatment nonadherence and nonpersistence to intravitreal anti-VEGF injections in nAMD.

Methods

This systematic review was conducted in accordance with the principles set out in the Cochrane Handbook for Systematic Reviews of Interventions.[12] The protocol for this systematic review was registered with the international PROSPERO database (ID: 172653) before data extraction. Our results and methods are presented in reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (http://www.prisma-statement.org, accessed 26 May 2019). All work adhered to the principles of the Declaration of Helsinki.

Eligibility Criteria for Considering Studies for This Review

Studies were eligible to be included in this systematic review based on the following criteria as set out in the Patient, Intervention, Comparator, and Outcome paradigm (Table 1). No eligibility restrictions were placed on the basis of the type of anti-VEGF used or the treatment regimen used. The minimum definitions of nonadherence and nonpersistence were not set in advance to allow for maximal inclusion of studies examining this topic. However, it was accepted that the term "nonadherence" was synonymous with "noncompliance." Likewise, the term "nonpersistence" was interchangeable with "discontinuation," "cessation," "lost to follow-up," or "dropout." Both quantitative and qualitative studies were eligible for inclusion to comprehensively address all aspects of the research question.

Studies were excluded if they assessed retinal conditions other than nAMD or evaluated interventions for nAMD other than intravitreal anti-VEGF injections. Conference abstracts were also excluded because of the inability to critically assess findings.

The primary outcome measure for this review was reasons or risk factors for treatment nonadherence and nonpersistence after at least 1 intravitreal anti-VEGF injection. Secondary outcome measures included efficacy of strategies to improve treatment adherence and persistence, as well as the rates of nonadherence and nonpersistence. Further assessments were made for factors that may be identified as general barriers to treatment.

Search Methods for Identifying Studies

The following databases were searched: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), clinicaltrials.gov online database, and Google Scholar. Databases were last searched and results updated on March 19, 2020. In addition, the reference lists from eligible studies were also reviewed to identify any additional suitable reports. No language restrictions were imposed, but if the report was not in English, the text was translated to allow for data extraction and full analysis of the risk of bias. There were no limits placed on publication date, but all studies had to be original and available in full. The search string for each database is provided in the Supplementary Material (Appendix and Table S1, available at www.aaojournal.org). References from the search results were imported into a reference management program (Zotero v5.0.66, open-source software, https://www.zotero.org).

Study Selection

After the database search, the studies were screened by appraising title and abstracts. Those studies that were considered to be consistent with the search criteria were analyzed in full text to confirm their eligibility. Two reviewers assessed the search results independently (M.O. and C.H.), and consensus was reached if there were any differences.

Data Collection and Quality of Evidence Assessment

Data from each eligible study were extracted and collected in a standardized Word (Microsoft Office, Microsoft Corp, Redmond, WA) document form (Table S2, available at www.aaojournal.org). Study origins and treatment setting (e.g., country, hospital clinic), patient demographics (e.g., age and baseline visual acuity), and treatment details including type of anti-VEGF and regimen used were recorded. Factors or correlates reported in the study relating to treatment nonadherence or nonpersistence were evaluated. Additionally, any strategies evaluated to improve the adherence or persistence were also extracted. The methodological quality of each study was assessed according to the Mixed Methods Appraisal Tool version 2018 because it can be used across qualitative, quantitative, and mixed-methods studies.[13] The overall quality and certainty of the evidence in the systematic review were evaluated using a modified GRADE approach to include qualitative evidence synthesis—the GRADE Confidence in the Evidence from Reviews of Qualitative Research tool.

Data Synthesis and Analysis

Rates of treatment nonadherence and nonpersistence, where available, were summarized with the proportion of patients reported for each outcome divided by the total number at risk in the reported study population. Results were reported individually for each study. Meta-analysis was not possible because of the variations in methodology for reporting outcomes across studies (e.g., differences in inclusion criteria with patient death, patient transfer for some studies but not others), differences in time period (total nonpersistence over several years vs. yearly rates), and lack of raw data for some studies to enable reanalysis. As an alternative, rates were tabulated according to each study and the data range provided. Factors for nonadherence and nonpersistence were also extracted from each study. These were broken down into 5 domains based on the standardized World Health Organization

Table 1. Eligibility Criteria Based on the PICO Strategy

	PICO Component	Inclusion Criteria	Exclusion Criteria
P	Patients	Studies including patients diagnosed with nAMD	Studies not reporting outcomes separately for patients with nAMD
I	Intervention	Patients received at least 1 intravitreal injection of ranibizumab and/or bevacizumab and/or aflibercept	Studies with patients receiving intravitreal injections other than anti-VEGF (e.g., triamcinolone) or other treatment (e.g., photodynamic therapy)
C	Comparison	Not applicable	Not applicable
O	Outcomes	1) Studies reporting the rates of NA/NP and factors for NA/NP 2) Studies addressing strategies to improve adherence and persistence 3) Studies assessing barriers to intravitreal therapy	No specific exclusions

NA = nonadherence; nAMD = neovascular age-related macular degeneration; NP = nonpersistence; VEGF = vascular endothelial growth factor.

multidimensions of adherence: (1) patient related; (2) condition related; (3) therapy related; (4) healthcare team and health system related; and (5) social/economic factors.[14] Factors were analyzed qualitatively according to theme, but also quantitatively with an odds ratio or percentage, where reported. Nonpersistence or nonadherence due to patient death or transfer of care was excluded from analysis. If possible, intentional discontinuation by treating physician from disease stability or remission was separated from unintentional nonpersistence in the analysis.

Results

Search Results

A total of 1436 studies were retrieved from the databases, yielding 1284 unique records after removal of duplicates. Initial screening of the titles and abstracts identified 124 potential studies for full-text review, with 35 remaining eligible after assessment of the full-text report. Two additional studies were identified via a manual search of the reference lists, with a total of 37 reports included in the final analysis. Figure 1 presents a Preferred Reporting Items for Systematic Reviews and Meta-Analyses—based flow diagram showing the number of records identified and excluded at each stage.

Studies were excluded for the following reasons: (1) did not examine nAMD specifically or included other interventions; (2) addressed other domains in health-related quality of life; and (3) cost-effective analysis or modeling of intravitreal injections on visual or quality of life outcomes without any correlation to impact on treatment adherence or persistence.

Study Characteristics

Of the 37 eligible studies, the majority (n = 33) assessed the factors for treatment nonadherence and nonpersistence, and a further 4 studies reported barriers to treatment without additional assessment of adherence and persistence.[15,16] Only 2 of the final studies explored strategies to improve treatment nonadherence and nonpersistence. Study characteristics are summarized in Table 2.

The studies were mainly European and US based, with a predominantly White population; only 3 reports involved patients from Asian countries.[17-19] The majority of studies assessed patients treated with intravitreal ranibizumab on a PRN dosing regimen, with a few more recent studies including intravitreal aflibercept or ranibizumab on a T&E regimen (Table 2). This reflects the timing of treatment initiation of these patients, with most receiving their first anti-VEGF injection before 2013 (Table S3, available at www.aaojournal.org). Most studies assessed patients treated in a tertiary hospital (university-affiliated hospitals or dedicated retinal clinic) as opposed to a local clinic (general comprehensive clinic) (Table 2).

Definitions

There was significant variation in the terminology and definitions of nonadherence and nonpersistence used across all studies. Definitions were not reported in some studies.[16,20,21] Synonyms used for nonadherence included "noncompliance,"[22,23] "absenteeism,"[24] and "nonattendance."[25] Synonyms for nonpersistence included "treatment discontinuation/cessation"[18,26,27] and "lost to follow-up"

Nonadherence was variably defined as follows:

- No treatment or consultation with a measure of visual acuity and OCT at least every 6 weeks[28]
- Extreme violation of prescribed treatment[22]
- Nonattendance of every clinic appointment[19]
- Receiving less than the recommended 8 injections over 12 months[25]
- Deviation from treatment recommendations (by patient or physician) with gap in treatment or consultation by more than 8 weeks[29]
- Visit outside of the prescribed 28 days ± 7 days window

Nonpersistence was variably defined as follows:

- Treatment discontinuation before 12 months,[30] study period,[26,27] or permanently[31]
- No treatment or visit at clinic for more than 4 months,[32] 6 months,[15,33,34] or 12 months[35,36]
- No follow-up by any ophthalmologist for 3 months[28]
- No follow-up within a 12-month period after receiving at least 1 anti-VEGF injection[37]
- Loss of follow-up of at least 24 months[18]

In some cases, intentional nonpersistence, either due to assessed treatment futility or treatment success with inactive disease, as agreed to by patient and treating physician, was not explicitly differentiated from patients who were lost to follow-up.

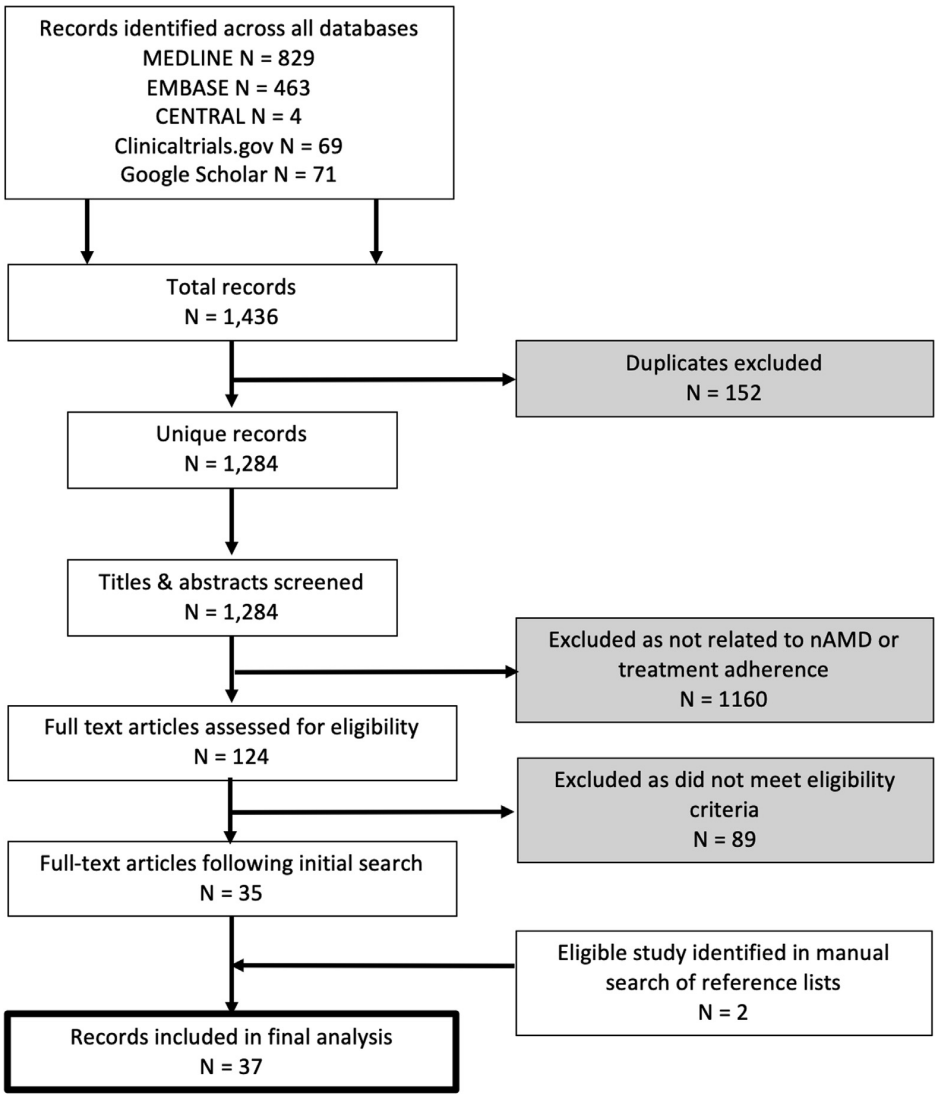

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses–based flow diagram of screening process. nAMD = neovascular age-related macular degeneration.

Prevalence of Nonadherence and Nonpersistence

Nonadherence to treatment or monitoring appointments was high with variable rates depending on how strictly it was defined (32%–95%).[25,28,29] In one study, which assessed nonadherence as no treatment or consultation at least every 6 weeks when using a PRN protocol, almost all patients (n = 346, 95.6%) fulfilled this criteria over a 12-month period, with a mean of 2.1 ± 1.1 gaps.[28] When determined by self-report however, rates of perceived nonadherence were lower, with patients in another study estimating their rates of nonadherence at 15.7% (n = 143) and caretakers estimating this at a higher 25.8% (n = 230).[19] Unsurprisingly, the observed rates of nonadherence were lower in a clinical trial setting, with a secondary analysis of the Comparison of Age-Related Macular Degeneration Treatment Trial reporting only 10.0% of 1060 patients not attending a study visit on time when defined as an average visit interval of 4 weeks ± 7 days over a 24-month period.[38] However, when the longest interval between 2 visits was calculated, 83.3% of patients still had at least 1 visit interval that was not on time.

Patients who discontinued treatment due to disease remission or treatment futility as judged by their physician accounted for 3% to 30% of all patients with nAMD who commenced treatment. After excluding these patients, the remaining rates of reported non-intentional treatment nonpersistence varied from 3% to 57% at 12 months, with lower rates when nonpersistence was defined as lack of follow-up visits rather than lack of anti-VEGF treatment.[35]

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