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Does Age-Related Macular Degeneration (AMD) Treatment Influence Patient Falls and Mobility? A Systematic Review

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Abstract

Purpose: Age-related macular degeneration (AMD), a leading cause of irreversible blindness, increases fall risk through impaired central vision. Falls place an enormous economic burden on healthcare systems. We hypothesized that AMD treatments may reduce patients' falls risk. This systematic review (ID #: 172623) synthesized the current understanding of wet and dry AMD treatments' impact on patient falls and mobility, connecting these two public health issues.

Methods: On April 17, 2020, PubMed, Scopus, CINAHL, and the Cochrane Library Clinical Trials Database were queried. Clinical trials and observational studies were included, while non-

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English and non-primary studies were excluded. Two authors screened, extracted data, and assessed bias using RoB-2 and ROBINS-I. A third author served as a tie breaker.

Results: This database search resulted in 3,525 studies, with an additional 112 identified through bibliography review. Ten articles met eligibility criteria. Most studies featured the outcome of interest as a secondary outcome (n=4) and patient-reported adverse events (n=5), rather than a primary focus (n=2). 10 out of the 11 outcomes had moderate to serious risk of bias. No two studies used the same instrument to measure falls or mobility.

Conclusion: Despite the potential positive impact of AMD treatments on patient falls and mobility, quality data on this relationship are lacking. This work underscores the need to broaden ophthalmologic research outcomes beyond visual parameters to include patient-centred, functional measures. Incorporating standardized methods to track falls and screen for difficulty with walking and balance would enable evaluation of AMD treatments on functional outcomes, potentially helping guide management.

Keywords: *Age-related macular degeneration, Anti-VEGF, photocoagulation, falls, mobility*

Introduction

Age-related macular degeneration (AMD), a leading cause of irreversible blindness in high-income countries, will increase in prevalence as the world's population ages. [1–4] This condition impairs central vision and contrast sensitivity which, in turn, increases fall risk. [5–7] Falls are a pervasive public health issue; world-wide, approximately 28-35% of people 65 and older fall annually, with 37.3 million falls requiring medical attention per year. [8,9] The United States Centers of Disease Control and Prevention estimates the financial burden of falls on the U.S. healthcare system to be approximately US$50 billion annually. [10] This substantial economic burden is not unique to the U.S., as the average cost per fall injury in Australia and Finland amounts to US$1,047 and US$3,611, respectively. [11,12] Independent of cost, falls are linked to poorer overall functioning and earlier admission to long-term care facilities. [13] Falls and limitations in mobility are significant predictors of worsening health status, functional dependence, and increased mortality; [14] they should not be considered an inevitable consequence of normal aging. [15]

Treatment, chosen based on type and severity of AMD, is geared towards reducing disease progression, vision loss, and perhaps vision improvement. [16] Reported outcomes are traditionally framed around visual parameters. Tracking the impact of these interventions on the frequency of patient falls and mobility is not typical, but may better reflect the impact of interventions on daily function and quality of life equal to or more than visual parameters. [17] Since AMD is likely to increase the risk of falls, treatment may mitigate this risk.

The objective of this systematic review without metanalysis, is to descriptively synthesize data on what is known about the relationship between AMD treatments (both established and

exploratory), patient falls and mobility and to emphasize the importance of including these outcomes in future research.

Materials and Methods

Data Sources

This systematic review (PROSPERO #: 172623) [18] was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines and adhered to the guidelines of the Declaration of Helsinki. [19] Given the nature of a systematic review, Institutional Review Board approval was not needed. A comprehensive search strategy was developed with the help of a research librarian. On April 17, 2020, PubMed, Scopus, CINAHL, and the Cochrane Library clinical trials database was searched with a combination of keywords and Medical Subject Headings (MeSH) (Table Supplement 1).

Study Selection

Included were primary, peer-reviewed studies. Excluded were review articles, editorials, commentaries, and articles not in English. We did not limit the search to a specific date range.

Two authors (H.G. and J.H.) independently screened identified titles for relevancy to the research question, with the aid of a tie-breaker (P.L.) who mediated study selection disputes. Our search focused on established and exploratory medical and surgical treatments for AMD, rather than tertiary prevention measures like visual rehabilitation or visual assistance devices. Because we predicted that falls and mobility measures, if considered, would likely be a secondary outcome in studies investigating AMD interventions, and therefore may be omitted from the title or abstract, we erred on the side of inclusion when screening titles for relevancy. The traditional abstract review was replaced by a full-text review for a predetermined list of terms using the "Find" tool to prevent erroneously excluding articles that addressed the research question (Table

Supplement 2). If the paper contained one word of interest from both the table's problem and outcome category, then the article was reviewed in full after ensuring proper context. For example, an article would be excluded if the word "stability" was used in the context of unchanged visual acuity in AMD participants, rather than physical stability, in the absence of other relevant outcome terms. If a full text could not be located, the authors of the publication were contacted up to two times to obtain the manuscript. If we still could not obtain a full text article, it was excluded.

Any clinical trials registration documents that were included after the title screen were read in its entirety. If the reviewers came to the consensus that the clinical trial pertained to our research question, then the resulting publication was assessed in its entirety. If a resulting publication was not listed, and one could not be identified through searching the selected research databases, then investigators were contacted about their findings.

Articles read in full that did not pertain to the research question were excluded. Figure 1 contains the study selection flow diagram with counts at each stage of study selection with reasoning for exclusion.

Reviews and other non-primary peer-review literature determined to be related to the topic but did not meet inclusion criteria ("grey literature") were later scanned for any potentially relevant sources not found in the initial search. Additional identified sources were subjected to the same selection process described above.

Data Extraction

Two-reviewers (H.G. and J.H.) independently extracted data from each study in the final sample. Information extracted included: citation information, study design, objectives, sample size, participant demographics, dropout rate, inclusion/exclusion criteria, and relevant findings.

Because there are no standardized or universal metrics for falls and mobility, no pre-identified summary outcome measures could be collected. Statistics, such as odds ratios, relative risks, and hazard ratios, were extracted if they were related to the outcome of interest.

Bias Assessment

Two reviewers (H.G. and J.H.) formally assessed study outcome bias using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I)[20] assessment tool and the revised Cochrane Risk-of-Bias tool for randomized trials (RoB2).[21] Authors came to a consensus on the risk of bias in the cumulative evidence

Synthesis of results

Authors with expertise in ophthalmology, epidemiology, public health, research methodology, and geriatric medicine, identified patterns and themes in the data extracted.

Results

Our search resulted in 10 peer-reviewed articles (Figure 1) with an aggregate 1,586 participants, described and assigned study numbers in Table 1. [22–35] All studies were published in the past 20 years (2005-2018), with half being randomized controlled trials (RCT's; n=5). The remaining articles included two cross-sectional studies, one prospective case series, one clinical observational study, and one prospective cohort study. Most studies featured the functional outcomes of mobility and falls as a secondary outcome (n=4) or as patient-reported adverse events during the trial period (n=5). Study #2 contained two relevant outcomes, resulting in a total of 11 findings within the 10 articles identified. [23] These articles were mostly published in ophthalmology journals (n=8). Most of these publications involved treatment interventions for patients with wet AMD (n=8), with only one exclusively studying dry AMD treatments (study #8) and one studying participants with either pathology (study #4).

There were a wide range of metrics used to measure falls and mobility, described in Table 6. Only one study, conducted by Szabo et al. (#9), used the currently accepted gold standard of falls reporting: prospective daily calendars with monthly follow up. [36,37] The rest were a mixture of validated (n=5) and non-validated (n=1) quality of life questionnaires, in-person tests, and falls reporting.

The therapies featured in these studies were the anti-vascular endothelial growth factor (anti-VEGF) therapies bevacizumab and ranibizumab (aflibercept was not included), photodynamic therapy, macular translocation surgery, and blue-light filter used in an intraocular lens.

The findings were not compelling, with 10 out of the 11 outcomes deemed to have a moderate to serious risk of bias. Table 2 displays the RoB-2 results for non-RCT's and Table 3

displays ROBINS-I results for RCTs. Of the 5 RCT's, only one study (#2) had established functional measures for patient mobility or falls. The remaining RCT's only included falls as patient-reported adverse events, which are largely underreported and pose a serious risk of bias. [38–41] Of all RCT's, mobility regularly assessed with the validated EQ-5D (study #2) was the only finding with a low risk of bias.

For the observational studies, moderate risk of bias was introduced in 4 out of the 5 publications, with the remaining one having a serious risk of bias. Particularly problematic ways of understanding impact on falls and mobility included only administering a questionnaire post-treatment (study #5 and #7) and using a non-validated questionnaire (#7).

A summary of evidence for the 10 studies can be found in Table 4. Interventions associated with improved mobility or decreased fall rates were found in the cohort study of community dwelling adults in Canada (#9) [29] and Nguyen's cross-sectional study of subjective physical functioning after macular translocation surgery in Germany (#7) [27]; both study findings have considerable limitations. Study #9 reported that among the group with neovascular AMD, 62% of injurious fallers vs. 81% of non-fallers were treated for this condition (p=0.021), suggesting that treatment could be associated with fall reduction. [29] The type of AMD treatment regimen was not specified and can be presumed to vary among study subjects. In study #7, the non-validated 9-question quality of life survey was administered only during their final post-operative visit, a procedure rarely performed now due to the advent of anti-VEGF injections. [27] Fifty-three percent of patients reported a good or very good subjective increase in visual function after surgery, but there was no pre-intervention mobility rating collected for comparison.

Only one study suggested a potentially negative relationship between treatment and mobility. Study #3 collected an Impact of Visual Impairment (IVI) profile, an instrument

assessing vision-related quality of life at baseline, 6, and 12 months for patients on ranibizumab injections. [24,42] Those who lost >2 lines on the retro-illuminated logarithm of the minimum angle of resolution visual acuity chart reported significantly worse on the mobility subscale at 12 months of treatment when compared to baseline (-1.66 on a Likert scale, SD ± 2.76, p=0.050). The remaining studies found no association between the treatment and functional measures, as described in the summary of evidence table (Table 4).

The time between intervention and functional assessment varied. The study that assessed mobility immediately after treatment used an in-person mode of measurement (#4, 15 days later). [25] Three studies assessed participant mobility up to 12 months after treatment with the use of questionaries (#3, 6, and 9). Three out of the four studies that followed participants up to 24 months only reported patient-reported adverse events (#1, 8, and 10). Some studies (#5 and 7) did not have a unified time interval between intervention and assessment for participants. [27,31]

Discussion

This systematic review unveiled 10 publications with heterogeneous study designs, methods, and findings. No two studies used the same assessment tool for evaluating falls or patient mobility. The majority of evidence presented in these papers is weak with a concerning risk of bias, making it impossible to remark on the relationship of AMD treatments on participants' mobility. This knowledge-gap is a red flag, considering there will be an inevitable increase in AMD and falls in the world's aging population. [1,43] If AMD treatments are shown to minimize fall risk by improving visual function, or for a different reason that could be explored, there will be broad benefits in adhering to AMD treatment recommendations, including improved quality of life, morbidity and perhaps mortality.

The first step in learning about how AMD treatments impact this resource-intensive, largely preventable burden on our healthcare system is to standardize measurement tools used in research to assess mobility and patient falls. Instead of listing falls and mobility as an unelicited, patient-reported adverse event, we believe that this outcome should be intentionally assessed. If feasible, we suggest requesting that patients complete a prospective "falls" calendar with monthly clinician check-ins, which is the current gold standard of falls reporting. [36,37,41] Eventually, this mode of falls assessment could be translated clinically into regularly asking patients over 65 years old if they fell during the past year or interval between ophthalmology appointments, as suggested by the American Geriatrics Society and British Geriatrics Society Clinical Practice Guidelines. [44] Using this method will more effectively utilize each healthcare contact to tackle this pervasive public health issue.

The Timed Up and Go test, which was not used by any of these studies, is a time-effective, accurate performance test that could be used to assess fall risk while studying AMD

interventions.[45] Participants taking 14 seconds or more to get out of their chair without using their arms, walking 3 meters, and returning to sit in their chair have an abnormal result.[46] An abnormal test demonstrates deficits in balance and gait, which are the most predictive risk factors for falls, and patients will need to be referred for a multifactorial falls risk assessment with their primary care provider.[44] Those who have difficulty with this test due to debilitating visual impairment or unsteadiness could be alternatively assessed using a validated questionnaire. Although one of the articles identified used an in-office obstacle course as a performance test, this is not pragmatic for widespread use in research.

Screening for risk factors or use of a validated instrument assessing fall risk is an alternative to performance-based assessments. Lee and Coleman advocated for the use of at least one instrument to define overall patient functioning when researching ocular treatments to demonstrate impact on important health outcomes.[17] The Best Practice Guidelines from ACS/NSQIP/American Geriatric Society also encourages postoperative assessment of fall risk factors through the use of a risk scale.[47] The Morse Fall Scale mentioned in these guidelines is a validated 6-question survey created to identify those with a high fall risk so preventive strategies can be employed. The Morse Fall Scale may be particularly useful in both ophthalmology research and clinical practice, due to its quick administration and negative predictive value of 99.3%.[48] None of the studies included in this review used the Morse Fall Scale or other ways to score identifiable risk factors. Studies should include these important health outcomes to demonstrate their efficacy, but there's no consensus on an optimal tool at this time.

In the current research, the majority of studies that include functional measures only record short-term sequela (≤ 12 months) of treatment on falls and mobility. Studies that extended beyond this time period only gathered falls as an adverse event. We hypothesize that a longer

interval of follow up might show an association between treatment and lower fall rates compared to those not receiving treatment. Furthermore, there might be varying strengths in association between treatment modalities at different time intervals. This additional benefit of the treatment, whether it be short-or long-term, could greatly enhance patients' quality of life.

The lack of widespread quality reporting on falls and mobility outcomes when investigating ophthalmic treatments is not unique to AMD research; a Cochrane Review similarly found that studies investigating the effect of behavioural and environmental interventions on falls and physical activity limitations in the visually impaired largely demonstrated poor methodological quality and heterogeneous outcome measures. [49] Given that a few high-quality studies have revealed important insights into the relationship between ophthalmic treatments and patient falls, including a potentially positive impact, additional relationships may be elucidated if properly studied. [50,51]

It is important to recognize that many factors can impact a participant's mobility, such as certain medications, comorbid conditions, and treatment adherence, complicating study design. [52] Most changes in gait in this age-group can be explained by underlying medical conditions progressing in severity. [15,53,54] In addition, patient treatment adherence is often worse in real-life circumstances than in randomized controlled trials; a factor which may further increase the patients fall-risk and mobility and decrease the effect that the ophthalmic intervention has on daily functioning. A combination of interventions for these medical conditions causing mobility impairment, including AMD, and promoting treatment adherence may prevent falls and loss of independence. [55,56]

Limitations to this review reflect an important finding; namely, falls and mobility outcomes are rarely assessed and reported in the current literature. Although the reviewers erred

on the side of inclusion, some primary studies answering our research question could have been erroneously excluded during the initial title screening step. To reduce the likelihood of this error, three individuals were involved in each step of the search process: two independent screeners and one adjudicator who held the deciding vote on inclusion discrepancies. In addition, we replaced the traditional abstract screening with searching the full-text using predetermined keywords to more effectively identify relevant articles. Although we tested these keywords on articles related to our research question, some relevant articles may have been missed if they did not use the chosen vocabulary. Other sources like Google Scholar and academic society's webpages may have revealed additional peer review articles not identified in these databases. Due to the high likelihood of redundancy and for practical purposes, this step was omitted. Other limitations include, but are not limited to, reporting bias and publication bias.

In conclusion, our study highlights the lack of quality data on how AMD treatments influence patient falls and mobility. If AMD treatments are shown to minimize fall risk by improving visual function, or for a different reason, there will be additional benefits to adhering to AMD treatment recommendations that impact not only visual function, but quality of life, morbidity and perhaps mortality. We are advocating to include standardized assessments of functional outcomes through validated instruments, falls tracking, or performance measures in research to better understand how ophthalmologists can do their part in tackling these pervasive public health problems.

Declaration of Interest Statement

The authors have no conflicts of interest to report.

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Table 1. Overview of reviewed studies

Study Number	Authors (year, country)	Title [Journal]	Study Design (setting, follow up time)	N (% AMD participants, type of AMD)	Intervention Investigated	Outcome related to falls/mobility [validated (V), not validated (NV) instrument, or not available (N/a)]
1	Antoszyk, A. N., Tuomi, L., Chung, C. Y., & Singh, A. (2008, USA)	*Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): Year 2 results* [American Journal of Ophthalmology]	Randomized, single-masked, controlled study (25 centers, 24 months)	162 (100%, wet AMD)	Photodynamic therapy + ranibizumab vs. photodynamic therapy + sham	Falls as adverse event (NV)
2	Chakravarthy, U., Harding, S. P., Rogers, C. A., Downes, S., Lotery, A. J., Dakin, H. A., et al. (2015, UK)	*A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to inhibit VEGF in age-related choroidal neovascularisation (IVAN)* [Health Technology Assessment]	Triple-masked randomized control study (23 centers, 24 months)	610 (100%, wet AMD)	Bevacizumab inferiority/non-inferiority trial to ranibizumab, continuous vs. discontinuous regimens	Mobility subscale of EuroQol- 5 Dimension (EQ-5D) questionnaire [V]; Falls as adverse event [NV]
3	Finger, R. P., Guymer, R. H., Gillies, M. C., & Keeffe, J. E. (2014, Australia)	*The impact of anti-vascular endothelial growth factor treatment on quality of life in neovascular age-related macular degeneration* [Ophthalmology]	Prospective "Case Series" (1 center, 12 months)	169 (100%, wet AMD)	Ranibizumab inject and extend protocol vs. every 4 weeks	Mobility subscale of 32-item Impact of Visual Impairment (IVI) questionnaire [V]
4	Kiser, A. K., Deschler, E. K., & Dagnelie, G. (2008, USA)	*Visual function and performance with blue-light blocking filters in age-related macular degeneration* [Clinical & Experimental Ophthalmology]	Clinical observational study (1 center, no follow up)	22 [44 eyes] (100%, AREDS 2,3, 4- wet and dry AMD)	No IR Medical's 751H filter wrapped around participants' habitual glasses (mimicking the spectral characteristics of the AcrySof Natural intraocular lens) vs. without	Number of "bumps" during mobility course [NV]
5	Krummenauer, F., Braun, M., & Dick, H. B. (2005, Germany)	*Clinical outcome and subjective quality of life after photodynamic therapy in patients with age-related macular degeneration* [European Journal of Ophthalmology]	Cross-sectional study (1 center, > 3 months (median= 9 months))	84 (100%, wet AMD)	Photodynamic therapy > 3 month prior	Mobility questions on Mainz questionnaire (in German) [NV]
6	Menon, G., Chandran, M., Sivaprasad, S., Chavan, R., Narendran, N., & Yang, Y. (2013, UK)	*Is it necessary to use three mandatory loading doses when commencing therapy for neovascular age-related macular degeneration using bevacizumab?* (BeMOc trial). [Eye]	Prospective randomized control trial (1 center, 12 months)	99 (100%, wet AMD)	No loading dose vs. 3 initial loading doses of bevacizumab in those treated with PRN	Falls as adverse event [NV]

7	Nguyen, N. X., Besch, D., Bartz-Schmidt, K., Gelisken, F., & Trauzettel-Klosinski, S. (2007, Germany)	*Reading performance with low-vision aids and vision-related quality of life after macular translocation surgery in patients with age-related macular degeneration* [Acta Ophthalmologica]	Cross-sectional study (1 center, last post-op (median= 11 months))	15 (100%, wet AMD)	Macular translocation surgery	Mobility question on 9-question quality of life survey [NV]
8	Rosenfeld, P. J., Dugel, P. U., Holz, F. G., Heier, J. S., Pearlman, J. A., Novack, R. L., et al. (2018, USA & Germany)	*Emixustat hydrochloride for geographic atrophy secondary to age-related macular degeneration: A randomized clinical trial* [Ophthalmology]	Randomized, double-masked, placebo-controlled, phase 2b/3 clinical trial (49 centers (USA), 7 centers (Germany), 25 months)	508 randomized, 503 treated, 320 completed the study. (100%, wet AMD)	Emixustat hydrochloride vs. placebo	Falls as adverse event [NV]
9	Szabo, S. M., Janssen, P. A., Khan, K., Lord, S. R., & Potter, M. J. (2010, Canada)	*Neovascular AMD: An overlooked risk factor for injurious falls* [Osteoporosis International]	Prospective cohort study (1 center, 12 months)	246, (21% dry AMD in the Non-NV AMD cohort, 100% wet AMD in AMD cohort)	No intervention	Falls tracking with prospective daily calendars and monthly follow-up [V]
10	Tano, Y., & Ohji, M. (2011, Japan)	*Long-term efficacy and safety of ranibizumab administered pro re nata in Japanese patients with neovascular age-related macular degeneration in the EXTEND-I study* [Acta Ophthalmologica]	Open-label, multicenter, Phase I/II study, extension phase (11 centers, 24 months)	70 (100%, wet AMD)	Ranibizumab 0.3 mg vs. 0.5 mg	Falls as adverse event [NV]

Table 2. RoB 2 Results for Included Randomized Trials.

Study Number	Measured Outcome	Randomization process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Section of the reported result	Overall
1	Falls as AE	+	!	!	-	-	-
2	Mobility subscale of EuroQol- 5 Dimension (EQ-5D) questionnaire [V]	+	+	+	+	+	+
2	Falls as AE	+	+	+	!	+	!
6	Falls as AE	+	!	+	!	-	-
8	Falls as AE	+	+	+	-	-	-
10	Falls as AE	+	+	+	-	-	-

Abbreviations: +, Low risk; !, Moderate risk; -, Serious risk.

Table 3. Robins-I Results for Included Non-Randomized Studies.

Study #	Measured Outcome	Bias due to Confounding	Selection Bias	Bias in classification of intervention group	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall Bias
3	Mobility subscale of 32-item Impact of Visual Impairment (IVI) questionnaire	+	+	+	+	++	++	++	++
4	Number of "bumps" during mobility course	+	+	++	+	+	++	+	++
5	Mobility questions on Mainz questionnaire	+++	+	+	+	+	+++	+	+++
7	Mobility question on 9-question quality of life survey	++	+	+	++	+	++	+	++
9	Falls tracking with prospective daily calendars and monthly follow-up	+	+	+	+	+	++	++	++

Abbreviations: +, Low risk; ++, Moderate risk; +++, Serious risk; ++++, Critical risk

Table 4. Summary of Evidence Table

Assessment Type (study #)	Intervention	Measurement Instrument used for Outcome of Interest (time of testing)	Outcome of Interest Result	Related Discussion	Related Study Limitations
Quality of life questionnaires					
(2)	Bevacizumab inferiority/non-inferiority trial to ranibizumab, continuous vs. discontinuous regimens after treatment at visits 0,1, and 2	EQ-5D (0, 3, 12, and 24 months)	No significant EQ-5D differences between groups (p = 0.74 for the drug comparison and p = 0.73 for the treatment regimen comparison)	No evidence of clinically important differences in EQ-5D utility	Mobility subscale results not reported
(7)	Macular translocation surgery	9-item quality of life questionnaire (assessed once at final post-op visit, median= 11 months after surgery)	53% good or very good subjective increase in visual function (not mobility specific), 40% no subjective change. No correlation between post-op visual acuity and mobility (p>0.1)	Participants were substantially concerned about their mobility-related issues. Visual function impacted quality of life, as demonstrated by significant correlations between dependency and mobility scores.	Non-validated. Did not administer questionnaire pre-op. Only one mobility question - didn't stratify results to mobility-specific visual function. This surgery is not the current standard of care.
(3)	Ranibizumab inject and extend protocol vs. every 4 weeks after 3 initial monthly injections	IVI questionnaire (baseline, 6, and 12 months)	At 6 months, no significant change in mobility at any strata. At 12 months, those who lost VA had significantly worse scores at for mobility, and no change or gain in VA had no significant change in mobility. Generalized linear models: no factors were associated with mobility subscales for the overall sample	A loss of VA led to poorer mobility (yet, gain of VA not associated with change in mobility)	Higher rate of attrition-patients were able to continue their treatment at a different provider at any time
(5)	Photodynamic therapy > 3 month prior	Mainz questionnaire (> 3 months after treatment, median= 9 months)	Mobility was not significantly associated with: subjective gain of vision clarity (p=0.528), subjective impression of mobility impairment progression (p=0.708), or clinically relevant change in visual acuity (r_s=0.28) since start of treatment. Those with > 3 lines lost in visual acuity showed an insignificant difference in mobility score on multivariate analysis (p=0.303).	Aspects of mobility were rated pessimistically; might be regarded as an AMD specific quality of life determinant.	PDT placebo effect. Confounded short-term and long-term benefit (no interviews before or shortly after)
In-person tests					
(4)	NoIR Medical's 751H filter wrapped around participants' habitual glasses (mimicking the spectral characteristics of the AcrySof Natural intraocular lens) vs. without filter	Mobility course (assessment visit only)	4% increase in number of "bumps" with NoIR filter, but not significant (p=?). Performance with and without the filter well correlated for mobility (r=0.66), with the regression slope not significantly different from unity (m = 1.16).	NoIR filter has no demonstrable clinically significant effect on mobility performance or risk. The mobility courses recreated situations in which older individuals with AMD may be more prone to bumps, decreased mobility or falls	Masking individuals to the intervention was not possible, but participants were split on perception of filter as hindering or enhancing performance.
Falls reporting					
(9)	Wet AMD and control group (includes dry AMD) cohort study- no intervention	Prospective daily calendars with follow-up by investigator (monthly)	In those with AMD, 62% of injurious fallers vs. 81% of non-fallers were treated p=0.021).	None	No mention of treatment type. Sample restricted to women in the community
(1)	Photodynamic therapy + ranibizumab vs. photodynamic therapy + sham	Patient-reported adverse event (anytime during study period)	Falls: control- 1 (1.8%), treatment- 0 (0%)	None	Only self-reported falls- not prompted
(10)	Ranibizumab 0.3 mg vs. 0.5 mg	Patient-reported adverse event (anytime during study period)	Falls: Single injection- 0.3mg (0%), 0.5mg (0%), Multiple injections- 0.3mg (3.6%), B 0.5mg (6.1%)	None	Only self-reported falls- not prompted

(8)	Emixustat hydrochloride vs. placebo	Patient-reported adverse event (anytime during study period)	Falls: emixustat 2.5 mg (5.3%), 5 mg (14.2%), 10 mg (9.7%), placebo: (15.8%), all emixustat (9.7%)	None	Only self-reported falls- not prompted
(6)	No loading dose vs. 3 initial loading doses of bevacizumab in those treated PRN	Patient-reported adverse event (anytime during study period)	Fall and radial fracture n=1 in no loading dose group, n=0 in loading dose group (adverse events recorded every 6 weeks)	None	Only self-reported falls- not prompted. Study dates not listed.
(2)	Bevacizumab inferiority/non-inferiority trial to ranibizumab, continuous vs. discontinuous regimens	Patient-reported adverse event (anytime during study period)	Falls: ranibizumab (2%), bevacizumab (1%); continuous (1%), discontinuous (2%); overall (1%)	None	Only self-reported falls- not prompted

Abbreviations: EQ-5D, EuroQoL-5 Dimension questionnaire; IVI, Impact of Visual Impairment questionnaire; VA, visual acuity; ?, unknown or not reported value.

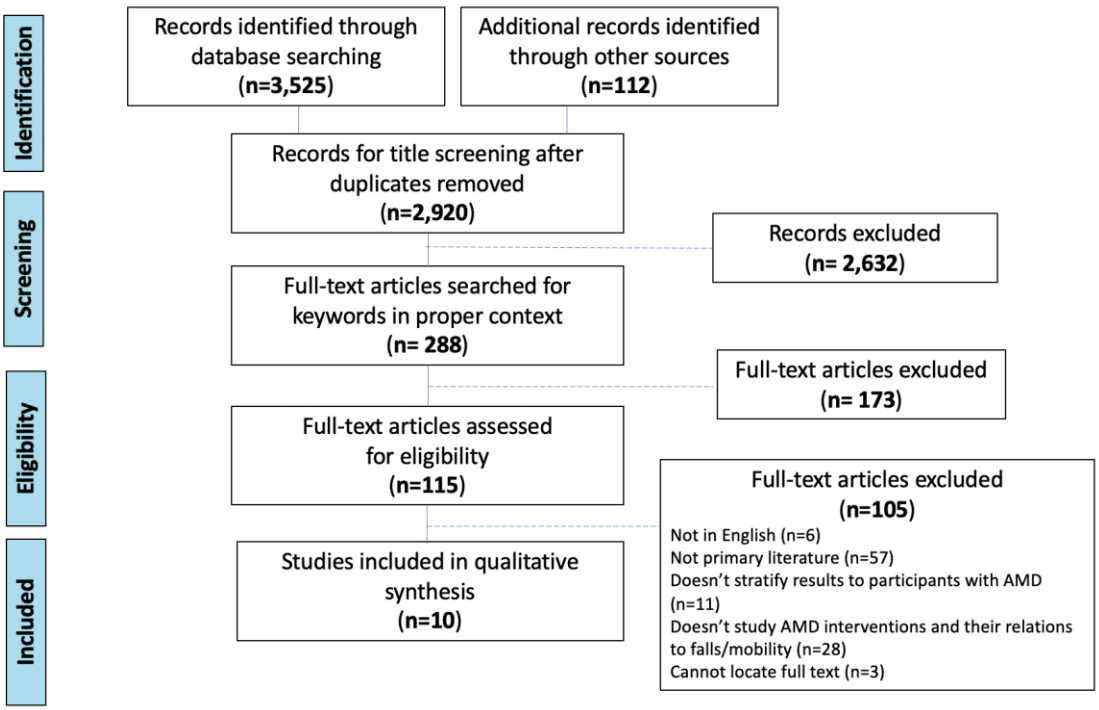

Figure 1. PRISMA Study Selection Flow Diagram