Review Article

Ethambutol optic neuropathy in the extended anti-tubercular therapy regime: A systematic review

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The extended use of ethambutol beyond 2 months for treating tuberculosis has increased risk of optic neuropathy. We performed a systematic review of studies evaluating optic neuropathy in extended ethambutol use since 2010 and compared the outcome with a similar systematic review (1965–2010) by Ezer *et al*. Literature search was conducted in PubMed, Medline, EMBASE, and Cochrane databases. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Main outcome measures were visual acuity, color vision, visual field defects, optical coherence tomography (OCT), and visual evoked potential (VEP). The JBI Critical Appraisal Checklists were used for quality assessment. Twelve studies were selected (out of 639 studies) for analysis of ethambutol optic neuropathy. Visual acuity improvement after stopping ethambutol was statistically significant. Similar improvement was not noted for other outcome measures. On comparing the results of this review with those by Ezer *et al*., significant improvement was noted in visual acuity, color vision, and visual field defects. Moreover, more patients reported increased optic nerve toxicity, color vision defects, and visual field defects in the present review. Hence, we conclude that the extended use of ethambutol beyond 2 months results in significant optic nerve toxicity. Further randomized controlled trials with different populations are needed to understand the magnitude of this issue.

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There are 10 million cases of tuberculosis (TB) reported globally.[1] Out of this, 26% cases are prevalent in India, with an incidence of 199/100,000 persons.[1] TB treatment is initiated with the DOTS regimen for both new and earlier treated cases of active TB without drug susceptibility testing.[2] It includes a 2-month intensive regimen of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB), followed by 4 months maintenance therapy of INH and RMP. Failure rate of this regimen was less than 1%, with a relapse rate of around 4%.[3] However, with increase in drug resistance, treatment guidelines were changed by the World Health Organization (WHO) in 2009 to include EMB in the maintenance phase.[3] In India, the Revised National Tuberculosis Control Program (RNTCP) incorporated this change in 2016, along with a change in dosing from thrice weekly to daily intake for 6 months.[4]

EMB is a potent antitubercular agent, but it is known to cause ethambutol-induced optic neuropathy (EON) in a dose- and duration-dependent manner.[2,5] The initiation dose prescribed by the WHO is 15–20 mg/kg body weight/day, which has an incidence of 1%–3% EON.[6] With an increase in the dose, EON increases to as high as 30% at 30 mg/kg/day, more so in patients with kidney dysfunction, uncontrolled diabetes, hypertension, age >65 years, and chronic smokers.[5-8] In developing countries, malnutrition and lack of awareness can lead to irreversible blindness with major socioeconomic consequences.[9]

The effects of EON were analyzed in a previous systematic review in 2013, with studies included till 2011.[10] However, there is a need to update and systematically review this data. Our review attempts to do so from 2010 to 2021, along with a comparison with the previous review.

Objectives

The three major objectives include the following:

1. Effect of EMB use on visual impairment (temporary and permanent)
2. Effect of risk factors (dose, duration of EMB, age) on the incidence of visual impairment
3. Extent of recovery after stoppage of EMB in these patients

Methods

a. Eligibility criteria

For objectives 1–3, any original study that measured visual acuity, color vision, Humphrey visual field (HVF), optical

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coherence tomography (OCT), and visual evoked potential (VEP) using standardized method was included. For Objective 3, measurements were done initially and at follow-up. The investigators ascertained if assessment was checked 1) routinely pretreatment, 2) in symptomatic patients, and 3) during treatment with EMB. Eligible studies included randomized controlled trials, cohort studies, prospective and retrospective case–control series, and case series with five or more patients. EMB regimen with dose and duration had to be clearly mentioned. Case reports, case series with less than five patients, reviews, abstracts, guidelines and recommendations, letters to editor and editorials, investigations-related articles, unpublished data, and management-related articles were excluded.

b. Information sources

We searched electronic databases of PubMed, Medline, EMBASE, and Cochrane reviews for original studies on EON during treatment of active TB. The reference lists of selected articles were reviewed for additional articles of relevance.

c. Search strategy

The search period was from January 2010 to December 2021. Key words included tuberculosis, TB, ethambutol, toxicity, optic neuropathy, ocular complications, visual impairment, and blindness. Initial review was done based on title and abstract. Selected articles were reviewed in a detailed manner for inclusion. Key search strategy used for PubMed from 01/01/2010 to 12/31/2021 were as follows:

(Ethambutol[mesh] OR optic[mesh] OR neuropathy*[mesh]): 463 articles
(Ethambutol[mesh] OR visual impairment*[mesh]): 584 articles
(Ethambutol[mesh] OR ocular complication*[mesh] OR blindness[mesh]): 107 articles
(Tuberculosis[mesh] OR Ethambutol[mesh] OR optic neuropathy*[mesh]): 391 articles
For comparison with data before 2010, we utilized the systematic review done by Ezer *et al*.[10] in 2013. All 22 articles selected in this study were re-evaluated. *Selection process-* It was done in three stages: study title, abstract, and full text. Two reviewers (SS and VG) independently extracted the data, compared them, and selected relevant studies. Any disagreement in study selection was resolved by consensus decision with all investigators. Articles in languages other than English were translated using Google translator online. For further clarification on total patient population treated by EMB during active TB, email communication was done as required with the first author of selected articles.

d. Data items (outcome)

The following parameters were recorded for every study: first author, country of study, number of patients on EMB, age, gender, TB regimen, EMB dose and duration, schedule of administration (daily vs. intermittent), methods and frequency of visual measurement, and the number of patients who started EMB, developed visual impairment, and had recovery measured. Results were stratified based on baseline and periodical assessment of same visual parameters.

e. Outcome definition

Reversible impairment: Decrease in visual acuity, color vision or defects in HVF, VEP, and OCT that resolved during follow-up

Permanent visual impairment: Decrease in visual acuity, color vision or defects in HVF, VEP, and OCT that did not resolve during follow-up

f. Synthesis methods

There were limited studies for comparison of dose and duration of EMB. The Joanna Briggs Institute (JBI) Critical Appraisal Checklists for case series, cohort study, case–control study, and prevalence study were used for the assessment of quality and risk of bias for each study.

g. Effect measurement

Effect sizes for all numerical variables were expressed as standardized difference in means with 95% confidence interval (CI). As the methodologies of the studies were heterogenous, meta-analysis was not planned. Statistical differences between the outcome measures were calculated using paired *t*-test ($P < 0.05$ was considered statistically significant). For comparing with previous data, Student's *t*-test was used, with $P < 0.05$ considered as the significant value.

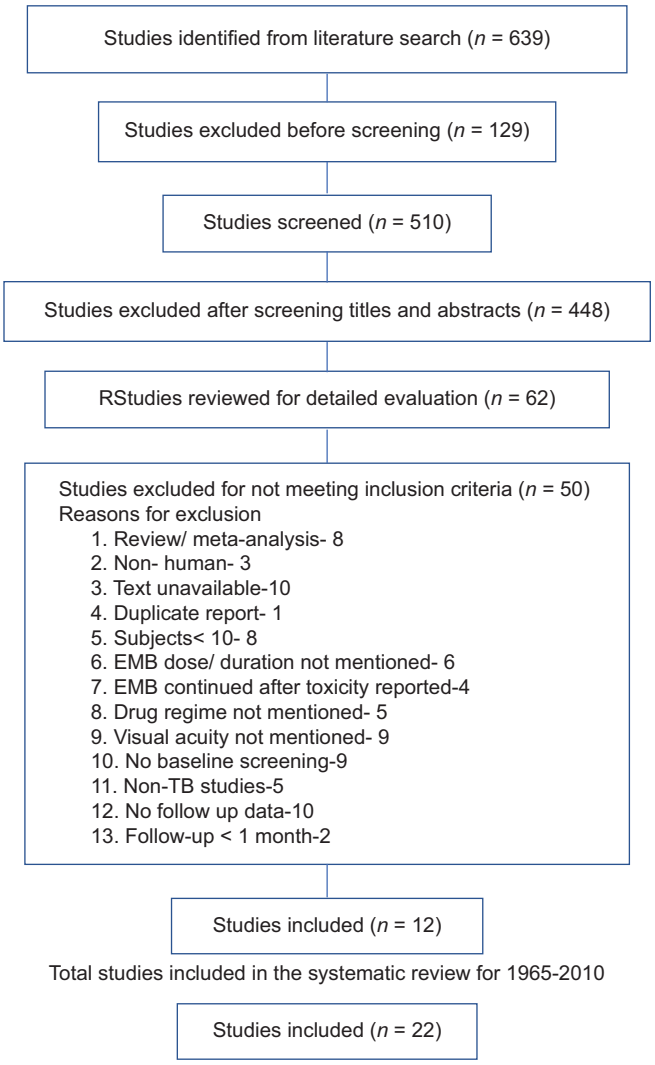

Figure 1: Flow chart for 2010–2021 systematic review of ethambutol optic neuropathy (*n* = number of studies). EMB = ethambutol, TB = tuberculosis

Table 1: Design of the studies

Author	Year of publication	Country	Study design	Total patients (*n*)	Patients with EON (*n*)	Average dose of EMB (mg/kg)	Follow-up duration (months)	Age (mean±SD)	Male: female (%)	Duration of ATT (mean±SD)	Duration of EMB (months)
Kim and Ahn[11]	2010	South Korea	Retrospective case series	7	7	17.5	6	61.3±13.8	43:57	7.57±1.5	7.5±1.39
Cumberland *et al.*[12]	2014	The United Kingdom	Surveillance study	36	12		6	68.5±9.75	50:50		11
Chen *et al.*[17]	2015	Taiwan	Retrospective case series	4803	62	16	6	70.02±14.1	66:34	5.94±4.06	5.94±4.06
Kim *et al.*[18]	2015	South Korea	Prospective case series	35	21	17	12	40.2±29.5	45:55	5	5
Garg *et al.*[20]	2015	India	Prospective cohort study	64	8		2	34.23±15.6	61:39	6	6
Lee *et al.*[19]	2016	South Korea	Retrospective case series	230	12	15	7	51.01±19.3	54:46	7.67±4.99	7.67±4.99
Kamii *et al.*[13]	2018	Japan	Retrospective case series	364	26	12.9			19:81		9.2
Taffner *et al.*[14]	2018	Brazil	Prospective case series	30	26		13	43.5±14.4	50:50		
Lee *et al.*[21]	2018	South Korea	Retrospective case series	21	21	18.9	12	59±12	43:57	5.7±2.9	5.7±2.9
Jin *et al.*[15]	2019	South Korea	Retrospective case series	114	50	14.7	8	45.5±17.2	47:53	4.31±2.42	4.31±2.42
Mandal *et al.*[16]	2020	India	Prospective case series	50	50	17.5	6	36.5±14.7	72:28	6	6
Shen *et al.*[22]	2021	China	Retrospective case-control study	64	14	15		52.28±19.9	57:43	7.43±2.53	5.6±4.0

EMB=ethambutol, EON=ethambutol optic neuropathy, ATT=antituberculosis therapy, SD=standard deviation

Table 2: Ophthalmological characteristics of the study population

Author	Baseline vision	Snellen acuity	Color vision	Ocular follow-up	Follow-up (months)	Total patients who stopped EMB due to visual symptoms (*n*)	Time to visual recovery on stopping EMB (months)	Total patients with complete visual recovery	HVF	Optic nerve pallor	OCT	VEP
Kim and Ahn[11]	Y	Y	N	Y	6	4	6	0	Y	Y	Y	N
Cumberland *et al.*[12]	Y	Y	Y	Y	6	12	3	2	Y	N	N	Y
Chen *et al.*[17]	Y	Y	Y	Y	6	16	8	0	Y	Y	N	Y
Kim and Park[18]	Y	Y	Y	Y	12	0		21	Y	Y	Y	N
Garg *et al.*[20]	Y	Y	Y	Y	2	6	6	6	Y	Y		
Lee *et al.*[19]	Y	Y	Y	Y	7		2	2	Y	Y	Y	N
Kamii *et al.*[13]	Y	N	N	N		25	13		N	N		
Taffner *et al.*[14]	Y	N	Y	Y	13		3	3	N	Y	Y	N
Lee *et al.*[21]	Y	N	Y	Y	12	21		0	Y	N	Y	N
Jin *et al.*[15]	Y	N	Y	Y	8	7	0		Y	Y	Y	N
Mandal *et al.*[16]	Y	N	Y	N	6	0	0		Y	Y	Y	Y
Shen *et al.*[22]	Y	N	Y						Y	Y	Y	N

HVF = Humphrey visual field perimetry, N = no, OCT = optical coherence tomography, VEP = visual evoked potential, Y = yes

Results

a. Study selection and characteristics

In total, 639 studies were identified, of which 62 were selected for detailed evaluation [Fig. 1]. After excluding 50 studies for not meeting the inclusion criteria, finally, 12 full-text articles were selected. Study characteristics and demographic features of the study population are summarized in Tables 1 and 2, respectively. Total number of patients was 5818, out of which 309 patients were diagnosed to have EON. Age of patients was 50.17 ± 13.86 years (mean ± standard deviation [SD]), while 607 cases were males. Of the 12 studies, six were retrospective case series, three were prospective case series, one each was retrospective case–control study and prospective cohort study, while one was a surveillance study.[11-22] All studies included patients with pulmonary TB. Five studies reported *Mycobacterium tuberculosis* as well as non-mycobacterial TB infection.[11-15] Comorbidities included renal failure and human immunodeficiency virus (HIV) infection.[13,15,17,19] Average dose of EMB was 16.06 ± 1.73 mg/kg body weight, with the range being 12.9–18.9 mg/kg body weight. Three studies did not mention the EMB dose schedule.[12,14,20] Mean (SD) duration of EMB usage was 6.72 ± 1.87 months, with a follow-up duration of 7.8 ± 3.3 months. Taffner *et al*.[14] did not report on the duration of EMB use. Table 3 shows the ophthalmological characteristics of each study. Baseline vision for both eyes was recorded for all studies; however, only 50% of the studies used Snellen charts, while two studies used Early Treatment of Diabetic Retinopathy Study (ETDRS) system.[14,16] Color vision was recorded by 10 studies.[12,14-22] HVF was done in 10 studies.[11,12,14-20,22] Optic nerve pallor was noted in nine studies.[11,14-20,22] OCT was used to measure retinal nerve fiber layer changes in eight studies.[11,14-16,18,19,21,22] Five studies used Cirrus OCT (Cirrus High-Definition Optical Coherence Tomographer; Carl Zeiss, Meditec, CA, USA), two used Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) while one study used Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA).[11,14-16,18,19,21,22] VEP was evaluated in three studies.[12,16,17]

b. Study outcomes

Outcomes measured in the 12 studies are given in Table 3.

i. *Effect on visual impairment*- Initial reduction in vision was reported in nine studies.[11-14,17,19-22] Improvement in vision did not occur in all patients after stopping usage of EMB in any of these studies. Two studies did not show initial reduction in vision, which remained consistent till the final follow-up.[16,18] Jin *et al*.[15] did not mention changes in visual acuity in their study. On excluding these three studies, there was a significant improvement in visual acuity on stopping EMB ($P = 0.035$).[15,16,18]

ii. *Effect on color vision impairment*- Initial reduction in color vision was reported in eight studies.[12-14,17,19-22] In four studies, there was complete recovery on stopping EMB,[12-14,20] while the remaining four studies showed partial recovery. Three studies did not find any color vision defect.[15,16,18] The improvement in this defect did not reach a statistically significant level ($P = 0.181$).

iii. *Effect on visual field defects*- Eleven studies reported defects in HVF,[11-13,15-22] with three studies showing complete reversal of the defects on stopping of EMB.[17,19,21] Two studies did not find any baseline defects on HVF in

Table 3: Initial and final outcomes after stopping EMB

Author	Initial reduction in vision (*n*)	Vision improvement on stopping EMB (*n*)	Initial color vision defect (*n*)	Improved color vison on stopping EMB (*n*)	HVF defects initial (*n*)	HVF defects on stopping EMB (*n*)	Optic disk pallor initial (*n*)	Optic disk pallor on stopping EMB (*n*)	Defects on VEP initially (*n*)	Defects on VEP on stopping EMB (*n*)	Defects on OCT initially (*n*)	Defects on OCT after stopping EMB (*n*)
Kim and Ahn[11]	7	5			7	7	5	7			7	6
Cumberland *et al*.[12]	4		7	7	5	5			6			
Chen *et al*.[17]	16	3	14	7	21				9			
Kim and Park[18]	0	0	0	0	0	0	0		21	21	21	21
Garg *et al*.[20]	6	0	8	8	4	4	6	6				
Lee *et al*.[19]	24	6	24	2	14		12				14	
Kamii *et al*.[13]	22	2	1	1	2							
Taffner *et al*.[14]	5	3	2	2				2			10	2
Lee *et al*.[21]	15	3	3	0	3	0	0	0	0	0	21	20
Jin *et al*.[15]	0		0	0	6	2					4	1
Mandal *et al*.[16]	0	0	0	0	0	0	0	0	28	3	28	3
Shen *et al*.[22]	14	0	3		14		1				14	

EMB=ethambutol, HVF=Humphrey visual field perimetry, OCT=optical coherence tomography, SD=standard deviation, VEP=visual evoked potential

Table 4: Comparison of values between systematic reviews of 1965-2010 and 2010-2021 (VEP and OCT values are not included as data are not available for the previous systematic review)

Parameter	Mean±SD (1965-2010)	Mean±SD (2010-2021)	*P*
Patients with EMB toxicity	11.33±1 8.09	25.75±17.60	<0.0001
Duration of EMB use	5.29±2.21	6.72±1.87	
Initial reduction of vision	11.28±18.72	9.41±8.15	0.0566
Vision improvement on stopping EMB	8.61±13.05	4.00±3.94	<0.0001
Initial color vision defect	3.33±3.72	5.63±7.12	<0.0001
Improved color vision on stopping EMB	1.7±2.1	2.70±3.13	<0.0001
Initial HVF defect	5.41±3.96	6.90±6.37	<0.0001
Improved HVF on stopping EMB	4.00±3.16	2.57±2.61	<0.0001
Total patients stopping EMB due to visual symptoms	6.07±4.66	10.11±8.47	<0.0001
Time to visual recovery on stopping EMB	4.43±2.58	4.55±3.94	0.6475
Total patients with complete visual recovery	4.36±3.11	4.25±6.60	0.7924

EMB=ethambutol, HVF=Humphrey visual field, OCT=optical coherence tomography, SD=standard deviation, VEP=visual evoked potential

Table 5: Comparison of values between initial examination and final examination for each outcome measure in systematic reviews 1965-2010 and 2010-2021

Parameters	1965-2010 (Mean±SD)	2010-2021 (Mean±SD)	*P* (1965-2010)	*P* (2010-2021)
Initial reduction of vision	11.28±18.72	9.41±8.15		
Vision improvement on stopping EMB	8.61±13.05	4.00±3.94	0.235	0.035
Initial colour vision defect	3.33±3.72	5.63±7.12		
Improved colour vision on stopping EMB	1.7±2.1	2.70±3.13	0.4525	0.181
Initial HVF defects	5.41±3.96	6.90±6.37		
Improved HVF on stopping EMB	4.00±3.16	2.57±2.61	0.18	0.175
Initial optic disc pallor	NA	3.43±4.20		
Reduced optic disc pallor on stopping EMB	NA	3.00±2.96		0.628
Initial OCT defects	NA	14.88±7.52		
Improved OCT on stopping EMB	NA	8.83±8.39		0.39
Initial defects on VEP	NA	12.80±10.22		
Improved VEP on stopping EMB	NA	8.00±9.27		0.72
Total patients stopping EMB due to visual symptoms	6.07±4.66	10.11±8.47		
Time to visual recovery on stopping EMB	4.43±2.58	4.55±3.94		
Total patients with complete recovery	4.36±3.11	4.25±6.60		
Incidence of improvement	NA	5.11±3.51		

SD=standard deviation, EON=ethambutol optic neuropathy, EMB=ethambutol, OCT=optical coherence tomography, VEP=visual evoked potential, ATT=anti tubercular therapy, HVF=Humphrey's visual fields, NA=data not available

their studies.[11,16] The reversibility was not statistically significant ($P = 0.175$).

iv. *Effect on optic disk pallor*- Only seven studies analyzed optic disk.[11,16,18-22] Three studies did not find any disk changes throughout the study period, while two noted increased disk pallor at the end of their study.[11,14,16,18,21] The changes did not reach a statistically significant value ($P = 0.628$).

v. *Effect on OCT findings*- Eight studies used OCT to analyze retinal nerve fiber layer.[11,14-16,18,19,21,22] In five studies, there was improvement in OCT findings after stopping usage of EMB.[11,14-16,21] Two studies did not specify the outcomes on final OCT on stoppage of EMB.[18,22] The difference in the values did not show statistical significance ($P = 0.39$).

vi. *Effect on VEP findings*- Five studies used VEP to analyze EON, out of which Lee *et al*.[21] did not report any VEP defect in their study.[12,16-18] On the other hand, Kim and Park[18] found no improvement in VEP after stopping EMB in their study. The outcomes were statistically not significant ($P = 0.72$).

vii. *Course of visual involvement during usage of EMB*- Nine studies reported on the total number of patients who stopped EMB intake due to visual symptoms, with a mean (SD) value of 10.1 ± 8.47.[11-13,15-18,20,21] Out of these studies, three studies did not find complete visual recovery in any patient on stopping EMB.[11,17,21] Kim and Park,[18] on the other hand, reported visual stability in all EON patients on stopping the drug. These patients had normal visual function at the study onset. Time to visual recovery varied between 2 and 13 months (mean ± SD of 4.55 ± 3.94).

c. Study quality assessment

The JBI Critical Appraisal Checklists were used for quality assessment of the studies (Supplementary Tables S1–S5). As the selected studies had heterogeneity in study design and

methodology and there was no randomized control trial, meta-analysis of the studies' outcome was not done.

d. Comparison of data with a previous systematic review

Ezer *et al*.[10] had systematically reviewed data published from 1965 to 2011 for EON (Group 1). The present study has attempted to compare it with the outcomes of the extended EMB regimen from 2010 to 2021 (Group 2). Table 4 shows the comparison of changes in vision, color vision, HVF defects, optic disk pallor, and OCT and VEP defects between the initial and final visits for each time period. Using Student's *t*-test, *P* value was found to be statistically significant only for vision improvement after stopping EMB usage in Group 2 ($P = 0.035$). Other outcome measures did not change significantly in either group.

Table 5 shows the comparison of outcomes between Group 1 and Group 2. There was statistically significant increase in number of patients having EON and patients stopping EMB due to visual symptoms in Group 2. The duration of EMB usage had also increased significantly since 2010.

When outcome parameters were compared, there was no significant change between groups 1 and 2 in the initial reduction of vision, time to visual recovery on stopping EMB, and patients reporting complete visual recovery in the final assessment. However, color vision defects on initial examination and initial HVF defects were significantly higher in Group 2. In contrast, improvement in visual acuity and HVF defects on stopping EMB usage was significantly higher in Group 1. Only the color vision showed significantly higher improvement in Group 2.

OCT and VEP changes were not recorded in Group 2 patients, hence were not compared with Group 1 patients.

Discussion

a. Interpretation

Since the onset of extended EMB regime, the risk of increased incidence of EON has been reported by multiple scientific groups.[5,6,9,23] The socioeconomic impact of visual impairment is high, more so in low-income communities which lack newer imaging technologies for detection of subclinical damage.[24] In this systematic review, we have reported only 35.4% patients recovering their vision on stopping EMB use, which was higher in the previous systematic review (70.9%).[10] Similar visual outcome have been reported in other studies.[25] Use of OCT and VEP in present times has improved the diagnosis of early optic nerve injury in vulnerable patients.[11,14,18,21,22,26] The present review recorded OCT changes in 119 patients, with improvement on stopping EMB observed in 53 (44.5%) patients. Improvement in VEP findings on stopping EMB was even lower at 37.5%. These results further validate the risk of EON with the extended EMB regime.

Although the EMB dose has been maintained around 15–20 mg/kg body weight since 1965, the duration of usage has progressively increased to as long as 12–18 months.[9,19,24] EON is known to be affected by increase in both the dose and duration of EMB.[6,9] Some studies reported residual visual defects at the final evaluation after stopping EMB.[11,12,17] This is a worrying trend as it contradicts the previous hypothesis that EMB causes reversible EON.[10,27]

b. Implications

The previous systematic review by Ezer *et al*.[10] had raised a very pertinent question of increased incidence of EON and risk of permanent blindness in 2.3 patients/1000 patients treated for 2–9 months with the current dose of EMB as per the WHO guidelines. The present review has demonstrated higher risk of visual impairment and irreversible EON. Use of this regimen in areas with poor ophthalmological services and higher incidence of TB might lead to lower detection of EON. Hence, the focus should be on baseline and follow-up visual evaluation during the treatment duration. A consensus statement and protocol for the baseline and follow-up evaluation of visual status of patients needing extended regimen of EMB has been given by Saxena *et al*.[28] Such a protocol should be followed diligently by both primary physician and ophthalmologist for every patient who is on EMB therapy. Patients having preexisting visual issues who need EMB therapy should be monitored with extra caution throughout the treatment period. Unfortunately, the present review shows a declining trend of robust studies, absence of randomized controlled trials, and lack of data on visual challenges of extended EMB therapy in HIV, renal insufficiency, and uncontrolled diabetes in the last decade. There is a need for well-designed prospective studies on different patient populations of the world to understand the visual and socioeconomic impact of EON.

c. Limitations of evidence

Unlike the previous review, there were no randomized controlled trials for planning a meta-analysis.[10] There was significant heterogeneity of the study populations. Renal parameters and immunodeficiency status were mentioned in only a few studies; therefore, we were unable to extract sufficient data from them. Visual acuity, color vision, and HVF are patient-dependent tests. Hence, the results were analyzed as "yes" and "no." This affected the measurement precision but was unavoidable in a heterogenous data set. Lack of data for the final outcome measures was encountered in some studies.[13,16,22]

Conclusion

This systematic review concludes that, as compared to the previous review by Ezer *et al*.,[10] the risks of visual impairment, color vision, and HVF defects with the extended EMB regime are higher. The findings should alert the medical community to this side effect of EON in vulnerable populations.

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Conflicts of interest

There are no conflicts of interest.

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