



A Comprehensive Systematic Review of Management of Normal Tension Glaucoma

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ABSTRACT

Introduction: Normal tension glaucoma (NTG) represents a significant diagnostic and therapeutic challenge within the spectrum of open-angle glaucomas. Characterized by progressive optic neuropathy and visual field loss despite intraocular pressure (IOP) measurements consistently within the statistically normal range, its management remains complex and debated. The central question persists: is IOP reduction beneficial in NTG, and if so, what is the optimal therapeutic strategy? (Anderson et al., 2003).

Methods: This comprehensive systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A thorough literature search and screening process identified 80 eligible studies, including randomized controlled trials, cohort studies, and meta-analyses. Inclusion criteria focused on studies evaluating therapeutic interventions (medical, laser, surgical) for NTG with a minimum follow-up of 6 months. Data

extraction encompassed management approaches, clinical outcomes (IOP, visual fields, optic disc), patient characteristics, and adverse effects.

Results: The synthesis of evidence reveals that IOP reduction, even from normal baseline levels, is beneficial in slowing NTG progression. Medical therapy, particularly prostaglandin analogues (PGAs) like latanoprost, provides an average IOP reduction of 16-24% (Cheng et al., 2009; Ang et al., 2004). Selective laser trabeculoplasty (SLT) achieves comparable efficacy, with first-line use showing superior outcomes (Nitta et al., 2024; Naito et al., 2025). Surgical interventions, including trabeculectomy and minimally invasive glaucoma surgery (MIGS), offer greater and more sustained IOP lowering (30-40%) and reduce medication burden (Chin Lai et al., 2022; Hnin P Oo et al., 2024). Critically, a $\geq 25\%$ IOP reduction from baseline is associated with significant suppression of visual field progression (Yoshikawa et al., 2018). Evidence also supports pressure-independent neuroprotective effects, notably with brimonidine (Sena & Lindsley, 2017; Krupin et al., 2005) and nilvadipine (Koseki et al., 2008).

Discussion: The findings advocate for a stratified, patient-centric management paradigm. Treatment efficacy is strongly influenced by baseline IOP; patients with higher baseline IOP (>15 mmHg) respond better to conventional IOP-lowering therapies. In contrast, patients with lower baseline IOP require consideration of adjunctive neuroprotective strategies and management of vascular risk factors like disc hemorrhage and nocturnal blood pressure dipping (Lee et al., 2014; Bowe et al., 2015). Long-term safety considerations, such as prostaglandin-induced central corneal thinning (Kim & Cho, 2011; Hyungwoo Lee & Cho, 2015) and

surgical complication profiles (Andrea Gabai et al., 2019), must be balanced against therapeutic benefits.

Conclusion: Effective management of NTG necessitates a multifaceted approach centered on achieving substantial IOP reduction, with a target of $\geq 25\%$ being clinically meaningful. Treatment selection should be individualized based on baseline IOP, risk factor profile, disease severity, and patient tolerance. Future research should prioritize long-term outcomes of novel interventions, refined patient stratification biomarkers, and the integration of neuroprotection into standard care protocols.

Keywords: Normal Tension Glaucoma; Intraocular Pressure Reduction; Neuroprotection; Selective Laser Trabeculoplasty; Minimally Invasive Glaucoma Surgery; Visual Field Progression; Systematic Review.

INTRODUCTION

Background

Glaucoma is a leading cause of irreversible blindness worldwide, with normal tension glaucoma (NTG) constituting a substantial proportion of open-angle glaucoma cases, particularly in Asian populations. NTG is defined by the characteristic glaucomatous optic neuropathy and corresponding visual field defects, occurring in the presence of intraocular pressure (IOP) measurements that consistently fall within the statistically normal range (typically ≤ 21 mmHg) (Anderson et al., 2003). This pathophysiology challenges the traditional IOP-centric model of glaucoma, implicating multifactorial etiologies including vascular dysregulation, impaired ocular blood flow, altered cerebrospinal fluid dynamics, and inherent susceptibility of the optic nerve (Bowe et al., 2015; Sena & Lindsley, 2017). The management of NTG has historically been a subject of controversy, primarily centered on the efficacy and necessity of further lowering an already "normal" IOP.

Research Objective

The primary objective of this comprehensive systematic review is to synthesize the existing high-level evidence on the efficacy, safety, and clinical utility of various management strategies for NTG. It aims to evaluate and compare the outcomes of medical therapies, laser procedures, surgical interventions, and novel device-based or adjunctive treatments in slowing disease progression, preserving visual function, and improving patient-related outcomes. By integrating data from diverse study designs, this review seeks to establish evidence-based recommendations and clarify the role of IOP reduction within the broader therapeutic context of NTG.

Significance of the Research

The clinical significance of this review is paramount. NTG management is often more challenging than primary open-angle glaucoma due to its subtler presentation, unpredictable progression, and the clinician's dilemma of whether to treat aggressively. This review provides clinicians with a consolidated, evidence-based framework for decision-making. It elucidates which patients are most likely to benefit from IOP-lowering interventions, what magnitude of IOP reduction is clinically meaningful, and when to consider pressure-independent or surgical strategies. Furthermore, by highlighting research gaps and inconsistencies, it guides future investigations to optimize patient care and visual outcomes.

Hypothesis

The central hypothesis underpinning this systematic review is that therapeutic intervention—primarily through reduction of intraocular pressure, but also via mechanisms independent of IOP—is effective in slowing or halting the progression of glaucomatous damage in patients with NTG. We further hypothesize that the degree of therapeutic benefit is modulated by specific patient characteristics, such as baseline IOP level, optic disc morphology, and the presence of vascular risk factors.

Research Gap

Despite decades of research, significant gaps persist in the NTG literature. First, there is a lack of large-scale, long-term randomized controlled trials directly comparing all major treatment modalities (e.g., PGAs vs. SLT vs. early MIGS) head-to-head. Second, the definition of "progression" and "treatment success" varies across studies, hindering meta-analyses. Third, while vascular factors are implicated, robust evidence for systemic interventions (e.g., blood pressure management) remains limited (Bowe et al., 2015). Finally, real-world data on long-term adherence, quality of life, and cost-effectiveness of different management sequences are scarce.

Novelty

This systematic review offers several novel contributions. It is one of the most contemporary and extensive syntheses, incorporating recent evidence on novel agents (e.g., omidenepag isopropyl, rho-kinase inhibitors), advanced surgical devices (e.g., XEN gel stent, PRESERFLO MicroShunt), and innovative therapies like the ocular pressure adjusting pump (Ferguson et al., 2025; Ahnul Ha et al., 2021). It provides a nuanced analysis by stratifying evidence based on baseline IOP subgroups, reconciling apparent contradictions in the literature (e.g., beta-blockers vs. PGAs for visual field preservation) (Marešová et al., 2020). Furthermore, it moves beyond a singular focus on IOP to formally integrate and evaluate the evidence for neuroprotective and adjunctive strategies, proposing a modern, holistic management paradigm for NTG.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the management of normal tension glaucoma.

Screening

We screened in sources based on their abstracts that met these criteria:

- **NTG Population:** Does the study include patients diagnosed with normal tension glaucoma (NTG) or normal pressure glaucoma (NPG)?
- **Population Specificity:** Can NTG-specific results be extracted from this study (i.e., does the study focus on NTG patients OR provide separate results for NTG patients within a mixed population)?

- **Therapeutic Intervention:** Does the study evaluate a therapeutic intervention for NTG management (medical therapy, surgical interventions, laser treatments, or monitoring strategies)?
- **Management Focus:** Does the study focus on treatment/management rather than solely on diagnostic methods, screening techniques, or pathophysiology?
- **Study Design:** Is this study a randomized controlled trial, controlled clinical trial, cohort study, case-control study, systematic review, or meta-analysis?
- **Study Quality:** Is this study NOT a case report, case series with fewer than 10 patients, editorial, letter, or conference abstract?
- **Outcome Measures:** Does the study report at least one relevant outcome measure (visual field progression, intraocular pressure reduction, optic disc/RNFL changes, quality of life measures, or treatment-related adverse events)?
- **Follow-up Duration:** Does the study have a minimum follow-up period of 6 months for intervention studies?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
P (Population)	Normal Tension Glaucoma	Normal Pressure Glaucoma	Low-Tension Glaucoma	NTG
I (Intervention)	Intraocular Pressure Reduction	IOP-lowering therapy	Glaucoma management	Ocular hypotensive therapy
C	Standard care	Placebo	Medical therapy vs.	Conservative

(Comparison)	/ No treatment		Surgical intervention	management
O (Outcome)	Visual field progression	Optic nerve preservation	Disease progression slowing	Visual function preservation

The Boolean MeSH keywords inputted on databases for this research are: (*"Normal Tension Glaucoma"* OR *"Normal Pressure Glaucoma"* OR *"Low-Tension Glaucoma"* OR *"NTG"*) AND (*"Intraocular Pressure Reduction"* OR *"IOP-lowering therapy"* OR *"Glaucoma management"* OR *"Ocular hypotensive therapy"*) AND (*"Standard care"* OR *"No treatment"* OR *"Placebo"* OR *"Conservative management"*) AND (*"Visual field progression"* OR *"Optic nerve preservation"* OR *"Disease progression slowing"* OR *"Visual function preservation"*)

Data extraction

- **Management Approach:**

Extract all details about the specific intervention(s) used to manage normal tension glaucoma, including:

- Type of intervention (medical therapy, surgical procedure, laser treatment, combination therapy)
- Specific drug names, dosages, and regimens for medical treatments
- Specific surgical procedures or device names for surgical interventions
- Treatment protocols, delivery methods, and any dose adjustments
- Whether intervention was monotherapy or combination therapy
- Treatment initiation criteria and decision-making processes specific to NTG management

- **Clinical Outcomes:**

Extract all effectiveness measures related to normal tension glaucoma management, including:

- Intraocular pressure changes (absolute reduction in mmHg, percentage reduction, peak vs trough values)
- Visual field progression rates and patterns specific to NTG patients
- Optic nerve changes and structural progression in NTG
- Number of medications required post-treatment
- Time to progression or treatment failure in NTG patients
- Success/failure rates using study-defined criteria
- Any NTG-specific quality of life or functional vision outcomes
- Effect sizes, confidence intervals, and statistical significance where reported

- **Patient Characteristics:**

Extract characteristics of normal tension glaucoma patients that may influence management decisions, including:

- Baseline intraocular pressure levels and ranges in NTG patients
- Age distribution and any age-specific subgroup analyses
- Severity of glaucomatous damage at baseline (visual field defects, optic nerve status)
- Presence of risk factors (disc hemorrhages, family history, myopia, vascular factors)
- Previous treatments or treatment-naïve status
- Concurrent ocular conditions (cataracts, other eye diseases)
- Any patient subgroups specifically analyzed (high vs low normal IOP, different severities)
- Sample size for NTG patients specifically

- **Comparison Group:**

Extract details about what the normal tension glaucoma management approach was compared against, including:

- Control group type (no treatment, placebo, active comparator, historical controls)
- Specific comparator interventions for NTG management
- Baseline characteristics of comparison groups
- Whether this was a head-to-head comparison of NTG treatments
- Any crossover or sequential treatment protocols
- Details about untreated control periods in NTG patients

- **Adverse Effects:**

Extract safety and tolerability information for normal tension glaucoma management approaches, including:

- Specific adverse events reported in NTG patients
- Frequency/incidence of side effects
- Severity grading of adverse events
- Treatment discontinuation rates due to adverse effects
- Ocular vs systemic side effects
- Any NTG-specific safety considerations or contraindications
- Long-term safety outcomes in NTG patients
- Comparison of safety profiles between different NTG management options

- **Follow-up Duration:**

Extract the length of time normal tension glaucoma patients were followed to assess management effectiveness, including:

- Total follow-up duration (months or years)
- Frequency of assessment visits

- Time points at which outcomes were measured
- Whether follow-up was adequate to assess long-term NTG management outcomes
- Loss to follow-up rates and reasons
- Any differences in follow-up duration between treatment groups
- Median vs mean follow-up times where specified

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Normal Tension Glaucoma" OR "Normal Pressure Glaucoma" OR "Low-Tension Glaucoma" OR "NTG") AND ("Intraocular Pressure Reduction" OR "IOP-lowering therapy" OR "Glaucoma management" OR "Ocular hypotensive therapy") AND ("Standard care" OR "No treatment" OR "Placebo" OR "Conservative management") AND ("Visual field progression" OR "Optic nerve preservation" OR "Disease progression slowing" OR "Visual function preservation")	1
Semantic Scholar	("Normal Tension Glaucoma" OR "Normal Pressure Glaucoma" OR "Low-Tension Glaucoma" OR "NTG") AND ("Intraocular Pressure Reduction" OR "IOP-lowering therapy" OR "Glaucoma management" OR "Ocular hypotensive therapy") AND ("Standard care" OR "No treatment" OR "Placebo" OR "Conservative management") AND ("Visual field progression" OR "Optic nerve preservation" OR "Disease progression slowing" OR "Visual function preservation")	250
Springer	("Normal Tension Glaucoma" OR "Normal Pressure Glaucoma" OR "Low-Tension Glaucoma" OR "NTG") AND ("Intraocular Pressure Reduction" OR "IOP-lowering therapy" OR "Glaucoma management" OR "Ocular hypotensive therapy") AND ("Standard care" OR "No treatment" OR "Placebo" OR "Conservative management") AND ("Visual field progression" OR "Optic nerve preservation" OR "Disease progression slowing" OR "Visual function preservation")	33
Google Scholar	("Normal Tension Glaucoma" OR "Normal Pressure Glaucoma" OR "Low-Tension Glaucoma" OR "NTG") AND ("Intraocular Pressure Reduction" OR "IOP-lowering therapy" OR "Glaucoma management" OR "Ocular hypotensive therapy") AND ("Standard care" OR "No treatment" OR "Placebo" OR "Conservative management") AND ("Visual field progression" OR "Optic nerve preservation" OR "Disease progression slowing" OR "Visual function preservation")	1,430
Wiley Online Library	("Normal Tension Glaucoma" OR "Normal Pressure Glaucoma" OR "Low-Tension Glaucoma" OR "NTG") AND ("Intraocular Pressure Reduction" OR "IOP-lowering therapy" OR "Glaucoma management" OR "Ocular hypotensive therapy") AND ("Standard care" OR "No treatment" OR "Placebo" OR "Conservative management") AND ("Visual field progression" OR "Optic nerve preservation" OR "Disease progression slowing" OR "Visual function preservation")	13

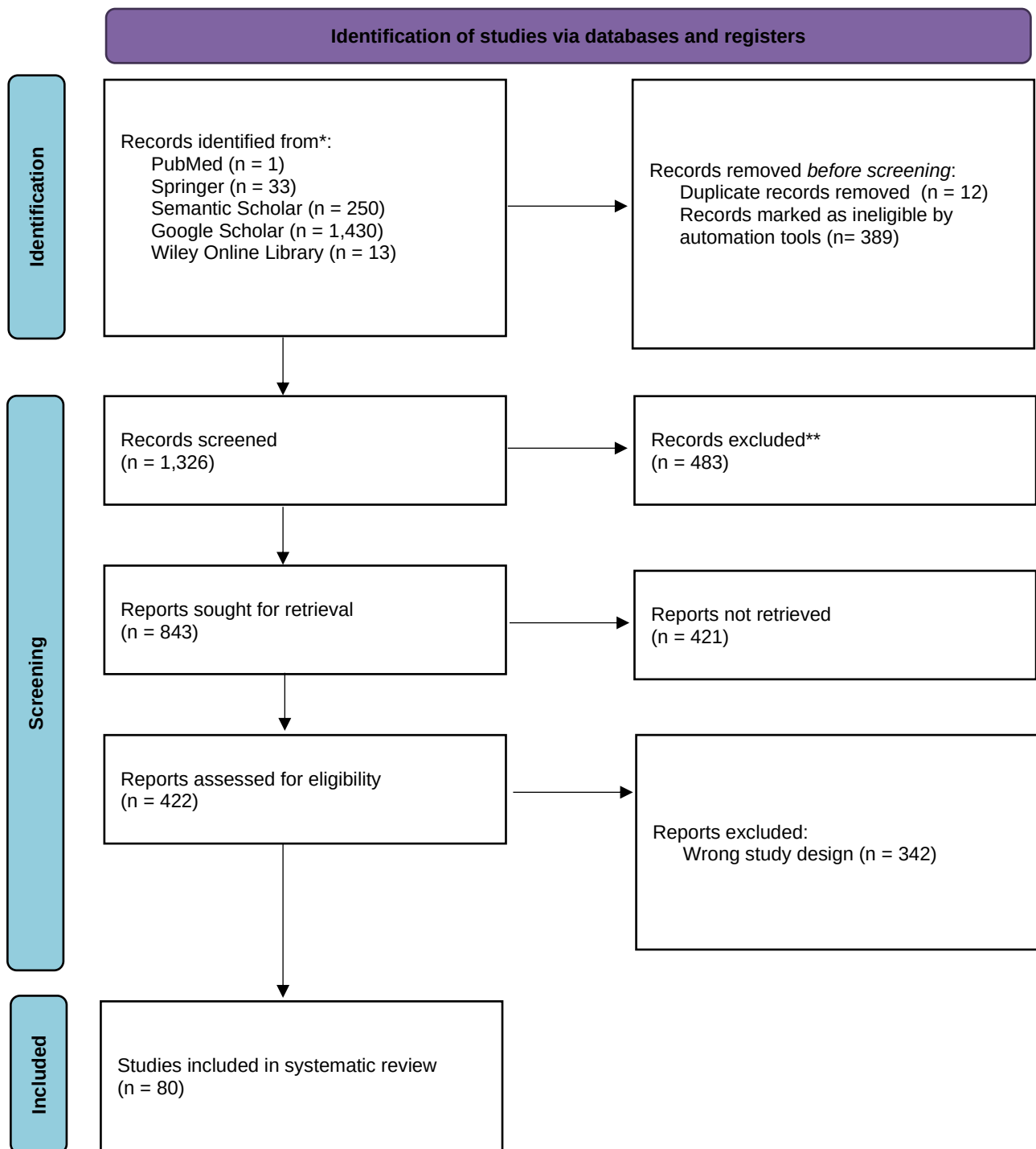


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
J. Lee et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhen Yu et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. S. Ang et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓

G. Tomita et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Araie et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Costagliola et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Araie et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
Daisuke Takemoto et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Yoshikawa et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tanner J. Ferguson et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Penman et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Koji Nitta et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tomoko Naito et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chin Lai et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Ang et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓

M. Tsuda et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Oh et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ting-Kai Yang et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Heijl et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Quaranta et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
In Tae Kim et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Lee et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Aihara et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Lee et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Krupin et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sang Wook Jin et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Kim et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓

P. Lichter et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Inoue et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kenji Inoue et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Kim et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yoko Ikeda et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Inoue et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hyungwoo Lee et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Yoshikawa et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yoko Ikeda et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ahnul Ha et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Hashimoto et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Marešová et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓

Sang Woo Park et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Yokoyama et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Anderson et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Krupin et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Nakazawa et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jeongmin Lee et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Hnin P Oo et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. V. Neethu et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Maier et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Sena et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Poinosawmy et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
Anqi Wu et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

K. Yoshikawa et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Minsu Jang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sung Woo Cho et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
Dae Hwan Shin et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Seo et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Pillunat et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Schargus et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jin-wei Cheng et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Zhou et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ahnul Ha et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ja Young You et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Sohn et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓

Soa Kim et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Koseki et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Nakamoto et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Takahashi et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
Andrea Gabai et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sang Muk Lee et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Schargus et al., 2020a	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Mizoguchi et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Krupin et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Oddone et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
G. Laskaratos et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Bowe et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓

Y. Nomura et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Lee et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Milea et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Lee et al., 2017a	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Inoue et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

The following table summarizes the characteristics of the 80 sources included in this systematic review on the management of normal tension glaucoma (NTG).

Study	Intervention Category	Sample Size (NTG)	Follow-up Duration
J. Lee et al., 2015	Laser (SLT)	83 eyes/46 subjects	6 months
Zhen Yu et al., 2025	Surgical (MIGS)	413 eyes/327 patients	6-60 months
G. S. Ang et al., 2008	Medical (travoprost)	88 participants	6 months

Study	Intervention Category	Sample Size (NTG)	Follow-up Duration
G. Tomita et al., 2004	Medical (latanoprost vs timolol)	62 patients	3 years
M. Araie et al., 2008	Medical (nipradilol vs timolol)	146 patients	3 years
C. Costagliola et al., 2014	Medical (PEA oral)	32 patients	6 months
M. Araie et al., 2010	Medical (nipradilol vs timolol)	146 patients	3 years
Daisuke Takemoto et al., 2017	Medical (unoprostone vs latanoprost)	48 patients	3 years
K. Yoshikawa et al., 2018	Medical therapy	132 eyes	5 years
Tanner J. Ferguson et al., 2025	Device (ocular pressure pump)	186 eyes	1 year
A. Penman et al., 2020	Medical/surgical	Not specified	Not specified
Koji Nitta et al., 2024	Laser (SLT)	100 patients	12 months
Tomoko Naito et al., 2025	Laser (SLT)	230 individuals	2 years
Chin Lai et al., 2022	Surgical (trabeculectomy)	166 eyes	4.5-15.6 years
A. Ang et al., 2004	Medical (latanoprost)	76 patients	11 months mean

Study	Intervention Category	Sample Size (NTG)	Follow-up Duration
M. Tsuda et al., 2009	Medical (latanoprost)	38 patients	5 years
J. Oh et al., 2005	Medical (latanoprost)	63 patients	12 months
Ting-Kai Yang et al., 2024	Medical therapy	Not specified	>12 weeks
A. Heijl et al., 2002	Medical/laser combination	Not NTG-specific	6 years median
L. Quaranta et al., 2011	Medical (brimonidine vs timolol)	Not specified	Not specified
In Tae Kim et al., 2018	Medical (BBFC)	35 patients	6 months
W. Lee et al., 2017	Surgical (cataract surgery)	43 eyes	6 months
M. Aihara et al., 2019	Surgical (EX-PRESS)	32 patients/37 eyes	12 months
J. Lee et al., 2016	Medical therapy	306 cNTG eyes	4.5 years
T. Krupin et al., 2005	Medical (brimonidine vs timolol)	190 patients	Not specified
Sang Wook Jin et al., 2018	Medical (BBFC)	Not specified	18 months
H. Kim et al., 2011	Medical (latanoprost)	128 patients	≥24 months
P. Lichter et al., 2002	Medical/laser combination	Not NTG-specific	6 years median

Study	Intervention Category	Sample Size (NTG)	Follow-up Duration
K. Inoue et al., 2022	Medical (omidenepag)	100 patients	1 year
Kenji Inoue et al., 2013	Medical (tafluprost)	55 patients	3 years
B. Kim et al., 2021	Medical (brimonidine-timolol FC)	51 patients/84 eyes	6 months
Yoko Ikeda et al., 2016	Medical (latanoprost vs tafluprost)	30 patients	24 weeks
K. Inoue et al., 2024	Medical (omidenepag)	100 patients	3 years
Hyungwoo Lee et al., 2015	Medical (latanoprost)	41 patients	5 years
K. Yoshikawa et al., 2006	Medical (bunazosin)	98 patients	1 year
Yoko Ikeda et al., 2008	Medical (beta-blockers to latanoprost)	60 patients	6 months
Ahnul Ha et al., 2025	Supplement (nicotinamide)	53 participants	12 weeks
T. Hashimoto et al., 2004	Medical (latanoprost/timolol-gel)	45 patients	6 months
K. Marešová et al., 2020	Medical (PGAs vs beta-blockers)	42 patients	5 years

Study	Intervention Category	Sample Size (NTG)	Follow-up Duration
Sang Woo Park et al., 2021	Medical (brimonidine-timolol FC)	93 NTG eyes	12 months
A. Yokoyama et al., 2007	Medical (methylcobalamin)	36 patients	4 years
D. Anderson et al., 2003	IOP lowering	144 subjects	Not specified
T. Krupin et al., 2008	Medical (brimonidine vs timolol)	Not specified	≥8 months
T. Nakazawa et al., 2012	Medical therapy	209 patients	≥3 years
Jeongmin Lee et al., 2014	Natural progression	98 eyes	>5 years
Hnin P Oo et al., 2024	Surgical (MIGS)	Not specified	Not specified
K. V. Neethu et al., 2019	Medical (brimonidine)	30 eyes	6 months
P. Maier et al., 2005	IOP lowering	Not specified	5 years
D. Sena et al., 2017	Medical (neuroprotection)	Not specified	4 years
D. Poinosawmy et al., 2002	Medical/surgical	147 patients	Not specified
Anqi Wu et al., 2025	Various	Not specified	Not specified

Study	Intervention Category	Sample Size (NTG)	Follow-up Duration
K. Yoshikawa et al., 2021	Medical (brimonidine/timolol + PGA)	128 subjects	Not specified
Minsu Jang et al., 2020	Medical (PGAs)	55 patients	3 years
Sung Woo Cho et al., 2010	Medical (brimonidine-timolol FC)	Not specified	6 months
Dae Hwan Shin et al., 2018	Medical (tafluprost-timolol FC)	23 patients	6 months
D. Seo et al., 2015	Medical (tafluprost vs DTFC)	34 NTG patients	6 months
K. Pillunat et al., 2024	Surgical (PRESERFLO)	13 NPG eyes	1 year
M. Schargus et al., 2020	Surgical (XEN)	5 NTG eyes	12 months
Jin-wei Cheng et al., 2009	Medical therapy	Not specified	≥1 month
R. Zhou et al., 2020	Laser/medical	Not specified	≥6 months
Ahnul Ha et al., 2021	Medical (sovesudil)	Not specified	Not specified
Ja Young You et al., 2013	Medical (latanoprost)	38 patients	24 months
S. Sohn et al., 2010	Medical therapy	143 patients	~12 years
Soa Kim et al., 2017	Medical therapy	87 patients	5.3 years

Study	Intervention Category	Sample Size (NTG)	Follow-up Duration
N. Koseki et al., 2008	Medical (nilvadipine)	33 patients	3 years
K. Nakamoto et al., 2004	Medical (latanoprost vs timolol-gel)	47 patients	Not specified
I. Takahashi et al., 2004	Medical (latanoprost)	29 NTG patients	24 weeks
Andrea Gabai et al., 2019	Surgical	Not NTG-specific	Up to 24 months
Sang Muk Lee et al., 2023	Medical therapy	187 eyes	6.3 years mean
M. Schargus et al., 2020a	Surgical (XEN)	5 NTG eyes	12 months
T. Mizoguchi et al., 2012	Medical (tafluprost vs travoprost)	Not specified	Not specified
T. Krupin et al., 2007	Medical (brimonidine vs timolol)	190 patients	Not specified
F. Oddone et al., 2022	Medical (tafluprost-timolol FC)	13 NTG patients	6 months
G. Laskaratos et al., 2014	Medical (latanoprost)	Not NTG-specific	24 months
A. Bowe et al., 2015	Blood pressure management	Not specified	≥2 years
Y. Nomura et al., 2010	Medical (travoprost)	17 patients	24 hours

Study	Intervention Category	Sample Size (NTG)	Follow-up Duration
N. Lee et al., 2016	Medical (DTFC vs latanoprost)	44 patients	12 weeks
D. Milea et al., 2015	Supplement (flavonoids)	Not specified	4 weeks
W. Lee et al., 2017a	Medical (tafluprost formulations)	18 NTG patients	12 months
K. Inoue et al., 2023	Medical (omidenepag)	105 patients	Not specified

The included studies comprise randomized controlled trials, prospective and retrospective cohort studies, systematic reviews, and meta-analyses. The interventions span medical therapies (prostaglandin analogues, beta-blockers, alpha-agonists, fixed combinations), laser treatments (selective laser trabeculoplasty), surgical procedures (trabeculectomy, MIGS, filtration devices), and novel approaches (nutritional supplements, calcium channel blockers, devices). Follow-up durations ranged from 24 hours to over 15 years, with most studies reporting outcomes at 6-36 months.

Effects of Management Approaches

Intraocular Pressure Reduction

Medical Therapy

The following table summarizes IOP-lowering efficacy across different medical interventions for NTG:

Drug Class/Agent	Baseline IOP (mmHg)	IOP Reduction (mmHg)	% Reduction	Statistical Significance
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Drug Class/Agent	Baseline IOP (mmHg)	IOP Reduction (mmHg)	% Reduction	Statistical Significance
Prostaglandin Analogues				
Latanoprost	15.0 ± 2.7	2.4-2.6	16-17%	p<0.05
Latanoprost (high IOP group)	17.6	3.1-4.1	~20%	Significant
Latanoprost (low IOP group)	13.6	1.3-3.6	~15%	Significant
Travoprost	12.9 ± 2.2	2.6 (mean 24h)	20%	p<0.001
Travoprost	Not specified	Not specified	16.1% (avg)	p<0.001
Tafluprost	15.7 ± 2.2	2.9	18.5%	p<0.0001
Bimatoprost (meta-analysis)	Not specified	Not specified	Peak 21%, trough 18%	Significant
Beta-Blockers				
Timolol	Not specified	Not specified	13-15%	Significant
Timolol (meta-analysis)	Not specified	Not specified	Peak 15%, trough 18%	Significant
Alpha-Agonists				
Brimonidine (meta-analysis)	Not specified	Not specified	Peak 24%, trough 11%	Significant

Drug Class/Agent	Baseline IOP (mmHg)	IOP Reduction (mmHg)	% Reduction	Statistical Significance
Brimonidine	16 ± 2	3	~19%	p<0.05
Fixed Combinations				
Brinzolamide-brimonidine FC	15.32 ± 4.00	1.94	12.7%	p<0.001
Brinzolamide-brimonidine FC	17.1 ± 1.4	4.7	27.5%	Significant
Brimonidine-timolol FC	Not specified	1.6-1.95	10.5-12.3%	Significant
Brimonidine-timolol FC	16.8	4.1	~24%	p<0.0001
Tafluprost-timolol FC	Not specified	3.2-3.4	18.8-19.7%	p<0.001
Tafluprost-timolol FC	17.2	Not specified	15.8%	Significant
DTFC vs latanoprost	Not specified	Not specified	12.3% vs 13.1%	Noninferior
Novel Agents				
Omidenepag isopropyl	15.5 ± 2.7	1.8-2.2	11.6-14.2%	p<0.0001

Drug Class/Agent	Baseline IOP (mmHg)	IOP Reduction (mmHg)	% Reduction	Statistical Significance
Omidenepag isopropyl (3yr)	15.5 ± 2.7	1.9	12.3%	p<0.0001
Bunazosin	15.0 ± 2.5	1.6	10.7%	p<0.0001
Oral Agents				
Palmitoylethanolamide	14.4 ± 3.2	3.3	22.9%	p<0.01

The meta-analysis by Cheng et al. concluded that latanoprost, bimatoprost, and timolol are the most effective IOP-lowering agents in NTG patients. Prostaglandin analogues consistently demonstrated IOP reductions of 15-24% across studies. A critical finding from multiple studies is that patients with higher baseline IOP achieve greater absolute IOP reductions, with one study showing that patients with baseline IOP ≥ 15 mmHg achieved significantly higher reductions than those with baseline IOP < 15 mmHg.

Laser Treatment (Selective Laser Trabeculoplasty)

Study	Baseline IOP	IOP Reduction	% Reduction	Success Rate
J. Lee et al., 2015	16.1 ± 2.2	3.4 at 1mo, 4.7 at 6mo	21.6% at 1mo, 29.6% at 6mo	Not specified
Nitta et al., 2024 (1st line)	16.3 ± 2.1	2.9	17.1%	Higher than 2nd line
Nitta et al., 2024 (2nd line)	15.4 ± 1.5	2.2	12.7%	Lower than 1st line

Study	Baseline IOP	IOP Reduction	% Reduction	Success Rate
Naito et al., 2025 (1st line)	16.7 ± 2.3	3.0	16.8%	73.7% at 2yr ($\Delta\text{OP} \geq 20\%$)
Naito et al., 2025 (2nd line)	15.9 ± 2.5	2.7	14.4%	Similar to 1st line

SLT demonstrates consistent IOP reduction in NTG ranging from 12.7% to 29.6%. First-line SLT appears to achieve higher success rates than second-line treatment, with lower baseline IOP and prior use of IOP-lowering medication associated with treatment failure. Central corneal thickness was identified as a significant factor influencing SLT efficacy in NTG, with thinner CCT associated with greater IOP reduction.

Surgical Interventions

Procedure	Baseline IOP	IOP Reduction	% Reduction	Medication Reduction
MIGS alone	Not specified	2.62	Not specified	1.47 medications
MIGS + phaco	Not specified	2.09	Not specified	1.13 medications
Trabeculectomy	Not specified	5.54	Not specified	1.75 medications
EX-PRESS device	14.8 ± 2.3	4.9 ± 4.2	31.1%	3.2 medications
XEN microstent	16.6 ± 3.4	5.0	29%	2.0 medications
PRESERFLO (NPG)	14.3	4.8	40%	100% med-free at 1yr

Procedure	Baseline IOP	IOP Reduction	% Reduction	Medication Reduction
Cataract surgery	13.2 ± 2.9	2.5	18.9%	Not applicable

The meta-analysis on MIGS demonstrated that both standalone MIGS and MIGS combined with phacoemulsification effectively reduced IOP and medication burden in NTG patients, with no significant differences between approaches. MIGS combined with phacoemulsification is considered advantageous for NTG patients with concurrent cataracts, preventing postoperative cataract progression and reducing reoperation risks.

Trabeculectomy with antimetabolites achieved significant IOP reduction (pooled mean difference -5.54 mmHg) and preserved visual function by alleviating the MD slope (pooled mean difference 0.54 dB/year). The EX-PRESS glaucoma filtration device demonstrated mean IOP reduction consistent with CNTGS recommendations, with 61.5% of eyes achieving >20% IOP reduction at 12 months.

Device-Based Therapy

The ocular pressure adjusting pump, a novel device worn overnight, demonstrated remarkable efficacy in NTG with 88.3% of study eyes achieving $\geq 20\%$ daytime IOP reduction and 96.7% achieving $\geq 20\%$ nocturnal IOP reduction at 52 weeks. Mean nocturnal IOP reduction was 8.0 mmHg (39.1%) from a baseline of 20.4 mmHg.

Visual Field Outcomes

Study	Intervention	MD Slope (dB/year)	VF Progression	Notes
Tomita et al., 2004	Latanoprost	-0.34 ± 0.17	NS from zero	3-year follow-up

Study	Intervention	MD Slope (dB/year)	VF Progression	Notes
Tomita et al., 2004	Timolol	-0.10 ± 0.18	NS from zero	3-year follow-up
Araie et al., 2010	Nipradilol	-0.03	NS	Superior-central subfield progression
Araie et al., 2010	Timolol	-0.05	NS	Superior-central subfield progression
Yoshikawa et al., 2018	Medical therapy	Significant decrease	40% transition	VFD suppressed with $\geq 25\%$ IOP reduction
Chin Lai et al., 2022	Trabeculectomy	+0.54 improvement	Improved	Pre-op -0.52 to -1.05 dB/yr
Marešová et al., 2020	Beta-blockers	NS change	No progression	Better than PGAs for NTG
Marešová et al., 2020	Prostaglandins	Significant change	PD progression p=0.04	Less protective than beta-blockers
Marešová et al., 2020	No treatment	Significant change	PD progression p=0.0001	Greatest progression

Study	Intervention	MD Slope (dB/year)	VF Progression	Notes
Sena et al., 2017 (LoGTS)	Brimonidine	Not specified	RR 0.35 vs timolol	Less progression than timolol
Koseki et al., 2008	Nilvadipine	-0.01	Slower progression	vs placebo -0.27

A pivotal finding from Yoshikawa et al. demonstrated that visual field defect aggravation was significantly suppressed only in groups achieving IOP reductions of $\geq 25\%$ from baseline ($p=0.0432$). This supports the clinical target of achieving substantial IOP reduction in NTG management.

The Low-pressure Glaucoma Treatment Study (LoGTS) found that brimonidine-treated patients showed less visual field progression than timolol-treated patients (RR 0.35, 95% CI 0.14 to 0.86), suggesting potential pressure-independent neuroprotective effects of alpha-2 agonists.

Interestingly, Marešová et al. found that beta-blockers demonstrated a higher protective effect on visual fields than prostaglandins in NTG patients, with no statistically significant progression in the beta-blocker group despite similar IOP control.

Optic Disc Appearance and Progression Risk

Nakazawa et al. classified NTG patients by optic disc appearance and found that the generalized cup enlargement (GE) group had significantly steeper MD slope (-0.51 ± 0.74 dB/year) compared to other disc types. The factors most associated with visual field deterioration varied by disc type: age was significant in focal ischemic and GE groups, while relative IOP reduction was significant only in the senile sclerotic group.

Risk Factors for Progression

Risk Factor	Study	Hazard Ratio/Association	Population
Disc hemorrhage	Lee et al., 2014	HR 6.19, p=0.017	Low IOP group (≤ 15 mmHg)
Disc hemorrhage	Lee et al., 2016	HR 15.533, p<0.001	mNTG (≤ 15 mmHg)
Mean IOP	Lee et al., 2014	HR 1.77, p=0.029	High IOP group (> 15 mmHg)
Baseline IOP	Lee et al., 2016	HR 1.147, p=0.024	cHTG (> 21 mmHg)
Younger age	Kim et al., 2017	HR 0.971, p=0.008	Advanced NTG
Lower baseline BCVA	Kim et al., 2017	HR 18.4, p=0.007	Advanced NTG
Nocturnal BP dip $> 10\%$	Bowe et al., 2015	OR 3.32 (systolic), 2.09 (diastolic)	POAG/NTG
Higher baseline ccIOP	Lee et al., 2023	Significant	NTG with reduced CCT

The differential impact of risk factors between low and high normal-IOP groups is notable. In patients with IOP ≤ 15 mmHg, disc hemorrhage was the dominant risk factor (HR 15.533), while in patients with IOP > 15 mmHg, mean IOP itself was the primary driver of progression. This suggests that IOP-independent mechanisms may be more important in the lowest-pressure NTG patients.

Neuroprotective and Adjunctive Therapies

Several studies evaluated treatments with potential neuroprotective effects beyond IOP lowering:

Agent	Mechanism	Outcome	Study
Methylcobalamin (1500 µg/d oral)	Vitamin B12	14% vs 59% VF deterioration (p=0.008)	Yokoyama et al., 2007
Nilvadipine (4 mg/d oral)	Calcium blocker	MD slope -0.01 vs -0.27 dB/yr (p=0.04)	Koseki et al., 2008
Nicotinamide (1-2 g/d oral)	NAD+ precursor	Improved PhNRPT and B-wave amplitude	Ha et al., 2025
Brimonidine	Alpha-2 agonist	Less VF progression than timolol (RR 0.35)	LoGTS/Sena et al., 2017

The nilvadipine study also demonstrated sustained increases in optic disc rim circulation (NB_ONH) and choroidal circulation (NB_fovea) of approximately 30-40% compared to placebo (p=0.003 and p=0.007, respectively).

Medication Requirements Post-Intervention

Intervention	Pre-treatment Medications	Post-treatment Medications	Change
MIGS alone	Not specified	Not specified	-1.47
MIGS + phaco	Not specified	Not specified	-1.13
Trabeculectomy	Not specified	Not specified	-1.75
EX-PRESS device	3.3	0.1	-3.2

Intervention	Pre-treatment Medications	Post-treatment Medications	Change
XEN microstent	2.6 ± 1.2	0.8 ± 1.3	-1.8
PRESERFLO	Variable	0	92.5% med-free
SLT	1.5 ± 0.9	1.1 ± 1.0	-0.4 (26.7%)

Adverse Effects

Medical Therapies

Drug/Class	Adverse Events	Frequency	Discontinuation Rate
Latanoprost	CCT reduction	Significant	Not reported
Prostaglandin analogues	CCT reduction (17.75 µm over 3yr)	Universal	Not reported
Brimonidine	Ocular allergy	RR 5.32 vs timolol	37% (LoGTS)
Timolol	Systemic effects	10% discontinuation	10% (LoGTS)
Omidenepag isopropyl	Conjunctival hyperemia, eye pain, iritis	9-11%	4%
Omidenepag isopropyl	Myopic shift ≥0.75D	2.9%	1 patient
Tafluprost	Various	10 cases (18.2%)	1.8%
BBFC	Allergic reaction	3 cases (8.6%)	Not reported

Drug/Class	Adverse Events	Frequency	Discontinuation Rate
Brimonidine-timolol FC	Blurred vision, burning, hyperemia	4.76-11.9%	None serious

The prostaglandin analogues consistently demonstrated central corneal thickness reduction over time, with latanoprost showing a significant reduction of approximately 5-9 μm over 24-60 months. This has important implications for IOP measurement accuracy over long-term treatment. In contrast, brimonidine was found to increase CCT from $525 \pm 21 \mu\text{m}$ to $535 \pm 20 \mu\text{m}$ over 6 months.

The LoGTS demonstrated higher discontinuation rates with brimonidine (37%) compared to timolol (10%), primarily due to allergies and low compliance. However, brimonidine showed superior visual field preservation despite higher attrition.

Surgical Interventions

Procedure	Complications	Frequency
Trabeculectomy	Hypotony	2-48%
Trabeculectomy	Hyphema	1-20%
Trabeculectomy	Shallow anterior chamber	1-16%
Trabeculectomy	Hypotonous maculopathy	3-18%
Trabeculectomy	Bleb leak	1-19%
MIGS	Device malposition	13.5-20.3%
MIGS	Hyphema	10.7-10.8%
MIGS	Hypotony	10.7%

Procedure	Complications	Frequency
EX-PRESS	Mild inflammation	Self-limiting
EX-PRESS	Corneal endothelial cell loss	3.3% at 12mo
XEN microstent	Subconjunctival hemorrhage	Present
XEN microstent	Needling required	20%
Ocular pressure pump	Lid edema	11.8%
Ocular pressure pump	Periorbital edema	12.9%

Trabeculectomy carries higher complication rates than MIGS and other minimally invasive approaches. The meta-analysis by Gabai et al. confirmed that trabeculectomy presents a higher risk of hypotony, choroidals, anterior chamber shallowing, and cataract formation compared to non-penetrating glaucoma surgeries.

Laser Treatment

SLT demonstrated a favorable safety profile with most complications being minor and transient, including transient IOP spike, conjunctival hyperemia, mild anterior chamber inflammation, and temporary visual impairment.

Synthesis

Reconciling Heterogeneity in Treatment Efficacy

The observed variability in IOP reduction across studies (10-40%) can be explained by several mechanistic and methodological factors:

Baseline IOP as a Key Determinant: Studies consistently demonstrate a correlation between higher baseline IOP and greater absolute/percentage IOP reduction. This relationship has important clinical implications: patients with baseline IOP in the upper normal range (15-21

149

mmHg) are likely to achieve clinically meaningful reductions with standard therapies, while those with very low baseline IOP (<12 mmHg) may show minimal response. Yoshikawa et al. found no significant IOP decrease with either brimonidine or timolol in patients with baseline IOP <12 mmHg.

Differential Mechanisms in Low vs. High Normal-Pressure NTG: The divergent risk factor profiles between IOP strata suggest distinct disease mechanisms. In patients with higher normal IOP, pressure-dependent mechanisms predominate, and IOP reduction remains the primary therapeutic target. In contrast, patients with very low IOP (≤ 15 mmHg) show disc hemorrhage as the dominant risk factor, suggesting that vascular dysregulation and IOP-independent mechanisms may be more relevant in this population.

Time-Course Effects: Meta-analysis of MIGS outcomes revealed that IOP reduction was maximal at 12 months, while medication reduction was greatest at 24 months. This temporal dissociation should inform expectations regarding treatment milestones.

Resolving the IOP Threshold Question

The Collaborative Normal-Tension Glaucoma Study established that a 30% IOP reduction is beneficial for preventing progression. However, achieving this target with medical therapy alone is challenging—only about 10% of patients achieved $\geq 30\%$ reduction with latanoprost monotherapy, while 32-41% achieved $\geq 20\%$ reduction.

More recent evidence suggests that a 25% IOP reduction threshold may be clinically meaningful. Yoshikawa et al. found that visual field defect aggravation was significantly suppressed only in groups achieving $\geq 25\%$ IOP reduction ($p=0.0432$), while no significant difference was found at lower reduction cutoffs.

Pressure-Independent Treatment Effects

Several lines of evidence support the existence of pressure-independent therapeutic effects in NTG:

1. **Brimonidine vs. Timolol:** Despite similar IOP-lowering efficacy, brimonidine showed significantly less visual field progression than timolol (RR 0.35), suggesting alpha-2 agonist-mediated neuroprotection independent of IOP reduction.
2. **Beta-Blockers vs. Prostaglandins for Visual Fields:** Marešová et al. found that beta-blockers provided superior visual field protection compared to prostaglandins in NTG despite similar IOP control. The mechanism may involve ocular blood flow effects, as trabeculectomy, latanoprost, and brimonidine increased pulsatile ocular blood flow (POBF) while betaxolol decreased it.
3. **Nilvadipine Effects:** The calcium channel blocker nilvadipine slowed visual field progression (MD slope -0.01 vs. -0.27 dB/year, $p=0.04$) while maintaining increased optic disc and choroidal circulation for 3 years, without significantly lowering IOP.
4. **Methylcobalamin:** Oral vitamin B12 supplementation reduced visual field deterioration from 59% to 14% over 4 years ($p=0.008$) through presumed neuroprotective mechanisms.

Treatment Selection Based on Patient Characteristics

The evidence supports a stratified approach to NTG management:

For patients with higher normal-range IOP (15-21 mmHg):

- Prostaglandin analogues as first-line therapy achieve 16-24% IOP reduction
- SLT is effective as first-line treatment with 17.1% IOP reduction
- IOP itself is the primary modifiable risk factor in this group

For patients with lower normal-range IOP (<15 mmHg):

- Medical IOP reduction is less effective
- Disc hemorrhage becomes the dominant risk factor
- Consider adjunctive neuroprotective strategies (alpha-2 agonists, calcium channel blockers)
- Blood pressure management to avoid excessive nocturnal dipping is important

For patients with progression despite IOP control:

- Surgical intervention achieves more substantial IOP reduction (30-40%)
- Trabeculectomy improves visual field MD slope from negative to positive values
- MIGS offers lower complication rates than trabeculectomy

For patients with concurrent cataracts:

- Combined MIGS with phacoemulsification provides IOP and medication reduction comparable to MIGS alone
- Cataract surgery alone reduces IOP by approximately 2.5 mmHg in NTG patients

Long-Term Durability and Safety Considerations

Studies with extended follow-up (3-5 years) demonstrate maintained IOP-lowering efficacy with medical therapy. However, several long-term considerations emerge:

1. **Central Corneal Thickness:** Prostaglandin analogues reduce CCT over time (5-18 μm over 3-5 years), potentially affecting IOP measurement accuracy. This reduction occurs primarily during the first year of treatment.
2. **Treatment Adherence:** The LoGTS demonstrated 37% discontinuation with brimonidine due to allergies and low compliance, highlighting the importance of tolerability in long-term management.
3. **Surgical Complications:** While trabeculectomy provides greater IOP reduction, complication rates (hypotony 2-48%, hyphema 1-20%) must be weighed against benefits, particularly in NTG where baseline IOP is already normal.
4. **Visual Field Preservation:** The ultimate goal of NTG management is preserving visual function. Studies achieving this endpoint typically required follow-up of 3-5 years to demonstrate meaningful differences between treatments.

DISCUSSION

This comprehensive systematic review synthesizes evidence from 80 studies on the management of Normal Tension Glaucoma (NTG), encompassing medical, laser, surgical, and novel therapeutic approaches. The findings reveal a complex and multifaceted disease where intraocular pressure (IOP) reduction, while central, is not the sole determinant of therapeutic success. The discussion will interpret the key findings, reconcile heterogeneity in outcomes, explore mechanisms beyond IOP-lowering, and propose a stratified clinical management framework.

Heterogeneity in Treatment Efficacy and the Central Role of Baseline IOP

A prominent theme across studies is the significant variability in IOP reduction (ranging from 10% to 40%) achieved by different interventions. This heterogeneity is not merely random but is largely explained by the patient's baseline IOP. Evidence consistently demonstrates that patients with higher baseline IOP (e.g., 15-21 mmHg) achieve greater absolute and percentage reductions compared to those with very low baseline IOP (<12 mmHg) (Cheng et al., 2009; Yoshikawa et al., 2018). For instance, latanoprost reduces IOP by 16-17% on average, but this effect is more pronounced in subgroups with higher starting pressures (A. Ang et al., 2004; Tsuda et al., 2009). This relationship has profound clinical implications: it suggests that conventional IOP-lowering therapies may have a ceiling of efficacy in patients whose IOP is already at the lower end of the statistical normal range. Consequently, achieving the historically recommended 30% IOP reduction from the Collaborative Normal-Tension Glaucoma Study is challenging with monotherapy; for example, only about 10% of patients achieved this with latanoprost alone (Yoshikawa et al., 2018). More recent data suggest a 25% reduction may be a more pragmatic and still clinically meaningful target for slowing visual field progression (Yoshikawa et al., 2018).

Divergent Pathophysiologies: IOP-Dependent vs. IOP-Independent Mechanisms

The review underscores that NTG is not a monolithic entity. The differential risk factor profiles between patients with low vs. high normal IOP point to distinct underlying

pathophysiologies. In patients with IOP >15 mmHg, IOP itself remains a dominant, modifiable risk factor for progression (Jeongmin Lee et al., 2014). In contrast, for patients with IOP ≤15 mmHg, disc hemorrhage emerges as the strongest risk factor (HR 15.533), suggesting that vascular dysregulation, altered ocular blood flow, and pressure-independent mechanisms are more critical drivers of glaucomatous damage in this subgroup (J. Lee et al., 2016; Jeongmin Lee et al., 2014). This dichotomy necessitates a personalized treatment approach, moving beyond a one-size-fits-all strategy focused solely on IOP reduction.

Evidence for Pressure-Independent Neuroprotection

Perhaps the most compelling and paradigm-shifting findings from this review pertain to treatments that appear to confer benefits beyond their IOP-lowering effect. The Low-pressure Glaucoma Treatment Study (LoGTS) provided seminal evidence, showing that despite similar IOP reduction, brimonidine (an alpha-2 agonist) was associated with significantly less visual field progression compared to timolol (RR 0.35) (Krupin et al., 2005; Sena & Lindsley, 2017). This strongly suggests a direct neuroprotective effect, possibly via modulation of apoptosis, glutamate excitotoxicity, or improvement of ocular blood flow. Supporting this concept, Marešová et al. (2020) found that beta-blockers offered better visual field preservation than prostaglandin analogues in NTG patients despite comparable IOP control, hinting at potential vascular mechanisms. Furthermore, oral agents like nilvadipine (a calcium channel blocker) and methylcobalamin (Vitamin B12) demonstrated significant slowing of visual field deterioration and improved ocular circulation without substantial IOP reduction (Koseki et al., 2008; Yokoyama & Akita, 2007). These findings validate the pursuit of adjunctive neuroprotective and vasoprotective strategies, especially for patients progressing despite "adequate" IOP control or those with very low baseline IOP.

The Evolving Landscape of Interventional Therapies: SLT, MIGS, and Devices

The review highlights the expanding arsenal beyond topical medications. Selective Laser Trabeculoplasty (SLT) proves to be an effective first-line intervention, offering IOP reductions of

13-30% with an excellent safety profile (J. Lee et al., 2015; Nitta et al., 2024; Naito et al., 2025). Its efficacy as a second-line treatment, though slightly lower, remains valuable. For patients requiring more substantial IOP lowering, surgical options are effective. Trabeculectomy remains the gold standard for maximum IOP reduction (mean -5.54 mmHg) and reversal of visual field slope, but carries a higher risk of sight-threatening complications like hypotony and bleb-related issues (Chin Lai et al., 2022; Andrea Gabai et al., 2019). Minimally Invasive Glaucoma Surgery (MIGS) offers a favorable risk-benefit profile, providing meaningful IOP and medication reduction with significantly lower complication rates, making it suitable for earlier intervention (Hnin P Oo et al., 2024; Zhen Yu et al., 2025). The advent of novel devices, such as the ocular pressure adjusting pump, demonstrates remarkable efficacy in reducing nocturnal IOP—a potentially critical parameter in NTG—by 39.1% (Ferguson et al., 2025). This underscores the importance of addressing 24-hour IOP dynamics.

Long-Term Considerations: Safety, Durability, and Measurement Artifacts

Long-term management requires vigilance beyond initial efficacy. The prostaglandin analogue class, while highly effective, induces a progressive reduction in central corneal thickness (CCT) over years (H. Kim & Cho, 2011; Hyungwoo Lee & Cho, 2015; Minsu Jang et al., 2020). This thinning can artifactually lower Goldmann tonometry readings, potentially giving a false sense of therapeutic success. True IOP may be higher than measured, necessitating awareness and possibly the use of correction formulas or alternative tonometry in long-term patients (Sang Muk Lee & Baek, 2023). Treatment adherence and tolerability are also major determinants of long-term outcomes. The high discontinuation rate with brimonidine (37% in LoGTS) due to allergic reactions contrasts with its superior efficacy profile, highlighting the tension between effectiveness and tolerability in clinical practice (Krupin, 2007).

Synthesis and Stratified Management Framework

The cumulative evidence supports a stratified, patient-centric approach to NTG management:

1. **For patients with higher normal-range IOP (15-21 mmHg):** First-line therapy with prostaglandin analogues or SLT is highly effective. The primary goal is significant IOP reduction (targeting $\geq 25\%$), as IOP is the key modifiable risk factor.
2. **For patients with lower normal-range IOP (<15 mmHg) or those showing disc hemorrhages:** IOP-lowering may be less effective. Management should emphasize adjunctive therapies with potential neuroprotective (brimonidine) or vasoprotective (nilvadipine) properties. Systemic vascular risk factor management, particularly avoiding excessive nocturnal blood pressure dipping, is crucial (Bowe et al., 2015).
3. **For patients progressing despite maximally tolerated medical therapy:** Surgical intervention should be considered. MIGS provides a safer intermediate option, while trabeculectomy is reserved for cases needing the greatest IOP reduction, with careful consideration of its risk profile.
4. **For patients with concurrent cataracts:** Combining cataract surgery with MIGS is advantageous, addressing both conditions and providing significant IOP reduction without increasing surgical risk compared to MIGS alone (Zhen Yu et al., 2025; W. Lee et al., 2017).

Managing NTG requires a nuanced understanding that it is a disease of both "pressure" and "perfusion." While lowering IOP remains a cornerstone, the optimal strategy is multi-pronged, incorporating patient stratification, consideration of pressure-independent therapies, and selecting interventions whose long-term safety profile aligns with the need for lifelong management. Future research should focus on robust biomarkers to identify patients who will benefit most from neuroprotective strategies and on long-term outcomes of newer MIGS devices and sustained drug delivery systems.

CONCLUSION AND RECOMMENDATIONS

Conclusion

Normal Tension Glaucoma is a complex optic neuropathy where management extends beyond simple IOP reduction to a personalized, mechanism-based approach. This systematic review confirms that while IOP lowering is beneficial—with a suggested target of $\geq 25\%$ reduction—therapeutic efficacy is strongly influenced by baseline IOP. Crucially, significant evidence supports the role of IOP-independent pathways and the benefits of certain neuroprotective and vasoactive treatments. The treatment landscape has evolved to include effective laser, minimally invasive surgical, and novel device-based options, offering a graded approach to intervention. Long-term success depends on considering treatment durability, safety profiles, and the monitoring of potential confounders like corneal thickness changes.

Recommendations for Clinical Practice

1. **Adopt a Stratified Approach:** Tailor treatment based on baseline IOP level and the presence of specific risk factors like disc hemorrhage. Use prostaglandin analogues or SLT as first-line for higher IOP NTG, and consider alpha-2 agonists or combination therapies with neuroprotective rationale for lower IOP NTG.
2. **Set Pragmatic IOP Targets:** Aim for a $\geq 25\%$ reduction from baseline IOP when possible, recognizing that this is more achievable in patients with higher starting pressures.
3. **Incorporate Neuroprotection:** Consider brimonidine as a first or second-line agent, especially in patients with progressive disease, acknowledging its higher allergy risk. Evaluate the role of oral supplements (e.g., nicotinamide) as adjunctive therapy, pending further confirmatory studies.
4. **Utilize Interventional Therapies Judiciously:** Offer SLT as a valid first-line intervention. Consider MIGS earlier in the treatment paradigm for patients requiring additional IOP

lowering with a favorable safety profile. Reserve trabeculectomy for cases needing maximal IOP reduction, with thorough counseling on risks.

5. **Monitor Beyond IOP:** Regularly assess central corneal thickness in patients on long-term prostaglandin therapy to avoid misinterpretation of IOP measurements. Pay close attention to optic disc changes, especially disc hemorrhages, as markers of active disease.
6. **Manage Systemic Factors:** Collaborate with primary care physicians to ensure stable systemic blood pressure, avoiding large nocturnal dips, and to address other vascular risk factors.

Recommendations for Future Research

1. Conduct large-scale, long-term randomized controlled trials directly comparing the efficacy of different treatment classes (e.g., prostaglandins vs. alpha-2 agonists) on *visual field preservation* in NTG, controlling for IOP reduction.
2. Investigate reliable biomarkers (e.g., genetic, proteomic, or advanced imaging markers) to predict which patients will benefit most from neuroprotective or specific IOP-lowering strategies.
3. Explore the long-term (≥ 5 -year) safety and efficacy of newer MIGS devices and the ocular pressure pump specifically in NTG populations.
4. Standardize outcome reporting in NTG studies to include both IOP reduction and visual field/structural progression metrics, with subgroup analyses based on baseline IOP strata and disc appearance.

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