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Old Drugs, New Roles: Non-Cardiac Uses of Beta-Blockers – An Updated Systematic Review

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Abstract

Background: β-adrenergic blockers (β-blockers) have long been used in cardiovascular medicine, yet growing evidence demonstrates significant therapeutic potential beyond cardiac disease. Their pleiotropic effects—ranging from modulation of sympathetic signaling to anti-angiogenic and immunomodulatory actions—have led to increasing interest in non-cardiac applications and drug repurposing.

Aim: To systematically review the non-cardiac roles of β-blockers, summarize recent findings (2020–2025), compare efficacy and mechanisms across clinical indications, and highlight emerging oncologic and immunomodulatory applications.

Material and Methods:This narrative review was conducted using PubMed, Google Schoolar and Scopus databases. Searches included the terms “beta-blockers”, “propranolol”, “timolol”, “non-cardiac”, “repurposing”, „glaucoma”, „hemangioma” and “oncology” for years 2020–2025. Included randomized trials, cohort studies, basic science papers with translational relevance, and meta-analyses. Articles unrelated to non-cardiac β-blocker mechanisms or without extractable outcomes were excluded.

Results: Non-selective β-blockers remain central in portal hypertension, reducing portal pressure and preventing variceal bleeding. In infantile hemangioma, oral propranolol demonstrates superior efficacy to topical timolol, with early treatment initiation strongly predicting success. Propranolol, timolol and metoprolol are effective in migraine prophylaxis, while propranolol remains a leading therapy for essential tremor, influencing both peripheral and central motor circuits. Timolol continues to be a cornerstone treatment in glaucoma, lowering intraocular pressure and delaying conversion from ocular hypertension to glaucoma. Emerging oncologic research indicates that propranolol may inhibit tumor proliferation, angiogenesis and immunosuppression, although clinical evidence remains heterogeneous.

Conclusions: β-blockers constitute a versatile, well-characterized class of drugs with validated non-cardiac indications and promising emerging roles, especially in oncology. Their broad mechanistic profile and established safety make them strong candidates for further clinical repurposing, but high-quality prospective trials are needed to define their oncologic relevance.

Keywords: β-blockers, hemangioma, portal hypertension, migraine, oncology

Introduction

Beta-adrenergic blockers (β-blockers) have been a cornerstone of cardiovascular medicine for more than half a century, traditionally prescribed for hypertension, ischemic heart disease, heart failure, and arrhythmias. Over time, however, growing evidence has revealed a remarkable therapeutic versatility that extends far beyond their classical cardiac indications. This expanding spectrum of non-cardiac applications reflects not only the pleiotropic pharmacological actions

of β-blockade—ranging from modulation of the sympathetic nervous system to effects on angiogenesis, intraocular pressure, and neurovascular tone—but also the increasing interest in drug repurposing as a strategy to improve clinical outcomes using well-characterized, low-cost agents.

Among the most well-established non-cardiac uses are the management of portal hypertension and the prevention of variceal bleeding in patients with chronic liver disease, where non-selective β-blockers such as propranolol, nadolol, and carvedilol reduce portal venous inflow and significantly lower bleeding risk. In pediatric dermatology, oral propranolol has revolutionized the treatment of infantile hemangioma, rapidly replacing systemic corticosteroids as first-line therapy due to its superior efficacy and safety profile. β-blockers also occupy an important place in neurology: propranolol and several other agents are widely used in migraine prophylaxis, while propranolol remains a cornerstone symptomatic therapy for essential tremor.

In ophthalmology, topical non-selective β-blockers such as timolol have long been a mainstay for reducing intraocular pressure in glaucoma and ocular hypertension. More recently, interest has turned toward the potential oncologic and immunomodulatory roles of β-blockade. Emerging preclinical and clinical data suggest that β-blockers may influence tumor proliferation, angiogenesis, metastatic potential, and the tumor immune microenvironment, raising the possibility of repurposing these agents as adjuncts in cancer therapy. [1]

Purpose

The purpose of this systematic review is to comprehensively evaluate and synthesize current evidence on non-cardiac uses of β-blockers, with a focus on studies published between 2020 and 2025. Specifically, this review aims to:

- Summarize established non-cardiac indications for β-blockers, including portal hypertension and variceal bleeding prevention, infantile hemangioma, migraine prophylaxis, essential tremor and glaucoma
- Identify and analyze emerging therapeutic roles, with particular emphasis on oncologic and immunomodulatory applications.
- Compare the efficacy, safety, and mechanisms of action across different β-blockers used for non-cardiac conditions.

- Highlight gaps in knowledge and propose future research directions to support evidence-based repurposing of β-blockers in clinical practice.

By integrating recent findings across multiple disciplines, this review seeks to clarify the evolving clinical relevance of β-blockade beyond cardiovascular medicine and to inform clinicians, researchers, and policymakers regarding its broader therapeutic potential.

Discussion

Non-selective β-blockers role in portal hypertension and prevention of variceal bleeding

Non-selective β-blockers reduce portal hypertension through combined β_1- and β_2-adrenergic blockade. Inhibition of cardiac β_1-receptors lowers cardiac output, thereby decreasing the volume of blood entering the splanchnic circulation. Simultaneously, β_2-receptor blockade removes β_2-mediated vasodilation within the splanchnic vascular bed, allowing unopposed α_1-adrenergic vasoconstriction to predominate, which reduces splanchnic blood inflow into the portal venous system. Carvedilol exerts an additional effect due to mild α_1-adrenergic antagonism, which can decrease intrahepatic vascular resistance. Together, these mechanisms lead to a reduction in portal venous pressure and lower the risk of esophageal variceal formation and bleeding.

In the study by Mullarkey [2], 2,302 patients with cirrhosis who were treated with non-selective β-blockers were evaluated, with 1,629 receiving carvedilol and 673 receiving propranolol or nadolol. After adjustment for baseline clinical differences, carvedilol therapy was associated with a lower risk of hepatic decompensation compared with propranolol or nadolol. Patients treated with carvedilol experienced fewer episodes of ascites, hepatic encephalopathy, and variceal bleeding, and the carvedilol group also showed a lower overall mortality. These differences were consistent across all decompensation outcomes evaluated.

In the comparative study by Joshi [3], carvedilol produced a significantly greater reduction in **hepatic venous pressure gradient (HVPG)** than propranolol. Carvedilol also led to a larger drop in **systemic vascular resistance (SVR)** and **mean arterial pressure (MAP)** than propranolol. Despite these hemodynamic differences, the medications demonstrated similar safety profiles, with no significant difference in the incidence of adverse effects between treatment groups.

The analysis by Jachs and Reiberger [4] further demonstrates that non-selective β-blockers

substantially reduce both first variceal bleeding and rebleeding in patients with portal hypertension. The reduction in portal venous pressure achieved with NSBB therapy was associated with improved clinical outcomes, including longer decompensation-free survival in compensated cirrhosis. In addition to hemodynamic benefits, NSBBs were linked to reductions in bacterial translocation and systemic inflammation, which may contribute to prolonged stability. The authors noted that the risk–benefit profile of NSBBs varies with disease severity, with greater caution required in advanced cirrhosis, while in compensated disease these agents support both effective bleeding prevention and maintenance of hepatic stability.

Infantile hemangioma — oral propranolol and topical timolol

Infantile hemangioma is a common vascular tumor of infancy that often grows rapidly during early life. Oral propranolol, a nonselective beta-blocker, is the established first-line therapy for lesions requiring treatment, particularly high-risk or complicated hemangiomas such as large lesions at risk of scarring or disfigurement, life-threatening hemangiomas, those that impair function, and ulcerated hemangiomas unresponsive to standard care. [5] Propranolol acts through rapid vasoconstriction of hemangioma vessels, suppression of angiogenesis by reducing VEGF and other pro-growth factors, and induction of apoptosis in proliferating endothelial cells, collectively slowing tumor growth and promoting accelerated regression.

Zhang et al., in a retrospective study of 207 infants with proliferative infantile hemangioma treated with oral propranolol, examined how age at treatment initiation, hemangioma risk status, and lesion subtype affected treatment success between months 6 and 12. Multivariate analysis identified age at treatment initiation ($P < 0.001$), high-risk hemangioma ($P = 0.002$), and segmental subtype ($P = 0.012$) as independent predictors of treatment failure. Receiver operating characteristic (ROC) curve analysis established optimal cutoff ages for initiating therapy: 69.5 days for all patients, 65.5 days for segmental or high-risk lesions, and 93.5 days for non–high-risk/non-segmental lesions. Infants who began propranolol therapy before 69.5 days achieved a success rate of 73.8%, compared with 28.4% for those who started later, and the median time to treatment success was 11.5 months versus 15 months, respectively. These findings indicate that early initiation of oral propranolol, particularly within the first 2–3 months of life, is strongly associated with higher success rates and faster resolution of infantile hemangiomas. [6]

A meta-analysis of seven studies including 2,071 infants with hemangiomas showed that oral propranolol had a higher overall response rate than topical timolol, but it was also associated with more adverse events. In the subgroup of superficial hemangiomas, timolol achieved similar

efficacy to propranolol while causing fewer side effects. When propranolol was administered at 2 mg/kg/day, it produced a markedly better response than timolol, whereas lower doses (1.0–1.5 mg/kg/day) did not show a significant difference in efficacy and were still linked to adverse events. [7]

Migraine prophylaxis — propranolol and other β-blockers

Beta-blockers, including nonselective agents such as propranolol and timolol, as well as selective ones like metoprolol, are established first-line treatments for migraine prophylaxis. Their preventive effects extend beyond cardiovascular actions. By blocking β_1-receptors, they reduce sympathetic outflow and noradrenaline release, lowering neuronal excitability, and may inhibit the trigeminovascular pain pathway via β-receptors in the thalamus. Propranolol has also been shown to suppress cortical spreading depression (CSD), a wave of neuronal depolarization implicated in migraine aura, reduce nitric oxide production via inhibition of inducible nitric oxide synthase (iNOS), and modulate serotonergic transmission through 5-HT_2B and 5-HT_2C receptors, thereby decreasing neurogenic inflammation and trigeminal activation [8,9].

Clinical evidence supports these mechanisms. A meta-analysis by Versijpt et al. [10], including 20 randomized trials with 1,291 participants, demonstrated that propranolol reduces monthly migraine days by an average of 1.27 days (95% CI, –2.25 to –0.30) compared to placebo. Furthermore, propranolol increased the proportion of patients achieving a ≥50% reduction in monthly migraine days, with a relative risk of 1.65 (95% CI, 1.41 to 1.93), corresponding to an absolute improvement of 179 per 1,000 patients (95% CI, 113–256). These findings highlight both the mechanistic rationale and clinical efficacy of β-blockers in migraine prevention.

β-Blockers in Essential Tremor

Propranolol reduces essential tremor primarily by blocking peripheral β-adrenergic receptors on muscle spindles, thereby decreasing the amplification of tremor oscillations. Owing to its lipophilic properties, it also crosses into the CNS, where it modulates cerebellar and motor-cortex activity, further contributing to tremor suppression. [11]

Recent neurophysiological research has provided clearer insight into how β-blockers, particularly propranolol, exert their effects in essential tremor. A 2024 TMS-based study showed that several months of propranolol therapy resulted in reduced corticospinal excitability and enhanced short afferent inhibition (SAI), a marker of improved inhibitory sensorimotor processing. These neurophysiological changes correlated with measurable reductions in hand tremor amplitude, indicating that propranolol's therapeutic effect involves both peripheral β-

receptor blockade and modulation of central motor circuits. Collectively, these findings support a dual mechanism of action and demonstrate meaningful functional benefits for patients. [12]

Further clinical evidence comes from a 2024 Bayesian model-based network meta-analysis of 33 randomized controlled trials involving 1251 patients, which compared 25 pharmacological and non-pharmacological treatments for essential tremor. Propranolol showed a significant improvement in tremor severity versus placebo (standardized mean difference –1.59, 95% CI: –2.25 to –0.67), placing it among the most effective therapies evaluated. Although the overall certainty of evidence was rated low to very low due to study heterogeneity, the results reinforce the clinical utility of propranolol and demonstrate that its combined peripheral and central mechanisms translate into substantial symptom reduction for many patients. [13]

Glaucoma and Ocular Hypertension – Topical Timolol

Topical timolol lowers elevated intraocular pressure (IOP) mainly by blocking β-adrenergic receptors on the ciliary epithelium of the ciliary body, which reduces the production of aqueous humor. This decrease in aqueous humor formation leads to lower IOP, alleviating pressure on the optic nerve and thereby reducing the risk of glaucomatous damage. [14]

The 2024 review by Patton and Lee offers a comprehensive overview of topical therapies used to lower IOP, emphasizing that pressure reduction remains the only proven method to slow glaucoma progression. The authors explain that non-selective β-adrenergic antagonists, particularly timolol, continue to play a central therapeutic role because of their strong ability to inhibit aqueous humor production. They highlight that topical delivery ensures high ocular bioavailability with limited systemic absorption—an important consideration for long-term safety in a chronic condition such as glaucoma. At the same time, they note that despite the proven efficacy of agents like timolol, treatment success relies heavily on tolerability and ocular-surface compatibility, especially regarding preservatives in multidose formulations. This underscores the importance of choosing an appropriate formulation to maintain patient comfort and achieve sustained therapeutic outcomes. [15]

Beyond its well-established mechanism of reducing aqueous humor production, long-term clinical data further illustrate timolol's role in preventing disease progression in high-risk patients. A prospective study in individuals with sustained ocular hypertension but without optic nerve damage demonstrated that those treated with topical timolol developed clinical glaucoma at a significantly lower rate over four to five years compared with untreated controls. This

suggests that timolol provides not only effective IOP reduction but also meaningful prophylactic benefit by delaying conversion from ocular hypertension to early glaucomatous disease. [16] Taken together, these findings reinforce the central therapeutic position of timolol in both the management and early prevention of glaucoma.

Oncology & immunomodulation

In recent years, non-selective β-adrenergic antagonists — especially **Propranolol** — have gained attention as potential adjuncts in cancer therapy. Preclinical and translational data suggest that β-blockade can inhibit tumor growth, reduce angiogenesis, and modulate the tumor microenvironment to support anti-tumor immune responses. For instance, in mouse models of fibrosarcoma and colon carcinoma, propranolol administration significantly slowed tumor progression, reduced tumor vascularization, enhanced infiltration of T lymphocytes, and decreased myeloid-derived suppressor cell infiltration; these effects enhanced the efficacy of immune-checkpoint blockade (e.g., anti-CTLA-4) in controlling tumor growth and metastasis. [17]

At the cellular level, propranolol has been shown to impair proliferation, migration and invasion of various cancer cell lines — for example, in gastric cancer lines propranolol induced G1-phase arrest, promoted apoptosis, and downregulated pro-angiogenic and matrix-remodeling mediators such as VEGF and MMP-2/9. Xenograft models confirmed significant reduction in tumor growth. [18] In colorectal cancer models, propranolol helped overcome chemoresistance: when given together with 5-fluorouracil, it disrupted hypoxia-adaptation pathways (e.g., reducing HIF1α and carbonic anhydrase IX), induced apoptosis, and slowed tumor growth, including in chemo-resistant cells. [19]

Epidemiological and meta-analytic data provide more mixed but nevertheless suggestive evidence that β-blocker use may influence cancer progression in humans. A large meta-analysis across nearly half a million patients found that β-blocker use was associated with improved progression-free survival (PFS), although no clear benefit was observed for overall survival (OS) or cancer-specific survival (CSS). [20]

On the basis of these data, β-blockers — in particular propranolol — represent an inexpensive, well-characterized class of drugs with a mechanistically plausible role in cancer repurposing. Their anticancer effects likely arise from a combination of direct inhibition of tumor cell proliferation and angiogenesis, modulation of hypoxia-associated survival pathways, and favorable remodeling of the immune microenvironment. However, clinical evidence remains

heterogeneous, and the benefits seem to depend strongly on tumor type, timing, combination therapy, and immune context — underscoring the need for prospective, well-designed clinical trials to clarify which cancer types and treatment regimens might most benefit from β-blocker repurposing.

Conclusion

This review demonstrates that β-adrenergic blockers possess a far broader therapeutic spectrum than their traditional cardiovascular indications suggest. Across multiple organ systems, β-blockers—particularly non-selective agents such as propranolol, nadolol, carvedilol, and timolol—exert clinically meaningful effects through well-defined mechanisms involving modulation of sympathetic activity, vascular tone, angiogenesis, and neurochemical signaling. Their established non-cardiac applications, including the management of portal hypertension, infantile hemangioma, migraine prophylaxis, essential tremor, and glaucoma, are supported by robust mechanistic rationale and a substantial body of clinical evidence.

Emerging research further highlights the potential of β-blockers in oncology, where adrenergic signaling contributes to tumor progression, angiogenesis, metastasis, and immunosuppression. Preclinical findings consistently show that β-blockade—particularly with propranolol—can inhibit tumor growth, enhance immune infiltration, overcome therapy resistance, and potentiate immunotherapy. While early clinical and epidemiological data suggest potential benefits, especially for progression-free survival, the evidence remains heterogeneous and insufficient to support routine oncologic use at this stage.

Taken together, the available data indicate that β-blockers represent a versatile, low-cost class of medications with both proven and emerging value in non-cardiac medicine. Their safety profile and widespread clinical familiarity make them compelling candidates for drug repurposing. However, key knowledge gaps persist, most notably the lack of prospective, high-quality clinical trials in oncology and limited comparative studies evaluating differential effects across individual β-blockers. Future research should aim to clarify patient selection, optimal therapeutic combinations, and mechanistic biomarkers in order to fully leverage the repurposing potential of β-blockers in modern clinical practice.

Disclosure

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