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Use of beta-blockers for rosacea-associated facial erythema and flushing: a systematic review and update on proposed mode of action.

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Capsule summary

- As treatment of rosacea-associated facial erythema and flushing is challenging, new therapeutic options are being explored. Beta-blockers may reduce erythema by vasoconstricting cutaneous vessels.
- Nonselective beta-blockers seem promising in treating erythema and flushing in rosacea that does not respond to conventional therapy, with most evidence available for carvedilol and propranolol.

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List of abbreviations

AE	adverse event
BID	twice daily
ETR	erythematotelangiectatic rosacea
F	female
M	male
ND	not described
OR	odds ratio
PPR	papulopustular rosacea
QD	once daily
RCT	randomized controlled trial
RR	blood pressure
TID	thrice daily

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Abstract

Background: Flushing and erythema are frequent skin symptoms in rosacea. As their adequate treatment remains a clinical challenge, new treatment options are explored, such as oral β-blockers.

Objective: To evaluate the efficacy of oral β-blockers for rosacea-associated facial flushing and erythema.

Methods: PubMed, EMBASE, Web of Science, and Cochrane Library were systematically searched, including studies providing original data on the efficacy of oral β-blockers in rosacea patients with facial flushing and/or persistent erythema. Risk of bias was assessed using the Cochrane Risk of Bias tool, Newcastle-Ottawa scale, and Quality in Prognosis Studies tool.

Results: Nine studies evaluating the use of carvedilol, propranolol, nadolol, and β-blockers in general were included. Articles studying carvedilol and propranolol showed a large reduction of erythema and flushing during treatment with a rapid onset of symptom control. Bradycardia and hypotension were the most commonly described adverse events.

Limitations: Most studies had a retrospective design with a small sample size, and outcome measurement was often subjective.

Conclusion: Oral β-blockers could be an effective treatment option for rosacea patients with facial erythema and flushing that does not respond to conventional therapy. Larger prospective trials with objective outcome assessment are needed to validate the promising results of these studies.

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Introduction

Flushing and persistent erythema are common rosacea symptoms.[1,2] In contrast to effective treatment options targeting inflammation in rosacea, diminishing erythema and flushing remains a clinical challenge.[3,4] The aetiology of increased blood flow in rosacea is complex and probably multifactorial; both vessel dilation, as well as neuronal, inflammatory, and hormonal pathways which can be enhanced by various external triggers seem to be involved.[5-7] The only approved treatments for facial erythema in rosacea are topical brimonidine and oxymetazoline, two selective α-adrenergic receptor agonists.[8-10] Although effective in some cases, poor response and rebound erythema are common, especially for brimonidine.[10-15] Their vasomotor target is however interesting, resulting in local vasoconstriction. As skin appearance has a significant impact on quality of life, the importance of new approaches for facial erythema and flushing has become clear.[16-18]

A possible not yet approved therapeutic option for persistent erythema and flushing are oral β-blockers. β-blockers antagonize the effects of sympathetic nerve stimulation and circulating endogenous catecholamines at adrenoreceptors.[19,20] Three types of adrenoreceptors exist; β_1-receptors are mainly located in the heart,[21] β_2-receptors in the lungs, gastrointestinal tract, blood vessels, and skin (keratinocytes, fibroblasts),[22-25] and α_1-receptors are amongst others found in smooth muscles of cutaneous blood vessels. In rosacea, β-blockers are believed to reduce erythema by blocking β_2-adrenergic receptors on smooth muscles of cutaneous arterial blood vessels, causing vasoconstriction.[26] Moreover, they may reduce anxiety and tachycardia, which can exacerbate flushing reactions.[27-30]

The aim of this systematic review was to elucidate the efficacy of oral β-blockers for flushing and persistent facial erythema in rosacea, and to provide recommendations for clinical practice.

Materials and Methods

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The study protocol was registered in PROSPERO (ID: 159025).[31] A systematic literature search following the PRISMA guidelines[32] was conducted in PubMed, EMBASE, Cochrane Library, and Web of Science. Search terms were *rosacea, flushing, facial erythema,* and *beta-blockers*, and all possible synonyms. Oral β-blocker types were extracted from a recent Cochrane review[33] and by exploring their MeSH-terms. Search strategy details can be found in Supplemental Table 1. We included studies conducted in adults with cutaneous facial rosacea that provided original data on use of oral β-blockers for rosacea-associated flushing and/or erythema (Supplemental Table 2). Physical modalities such as laser therapy also act on the vascular component, but are out of scope of this paper.[3,34]

All databases were searched to include published studies from date of inception until 20 November 2019. Titles and abstracts were screened for relevance by two independent reviewers (JGML and JIO). Next, full texts were critically assessed for eligibility by the same reviewers. Missing full texts were requested via the Radboud University Medical Library. In both phases, differences between the reviewers regarding inclusion were resolved by discussion. Excluded were papers involving: patients <16 years old; ocular, extrafacial or drug-induced rosacea; drug-induced flushing; *in vitro* and animal studies; studies in languages other than English, German or Dutch; meta-analyses, (systematic) reviews, and abstracts of congresses or with unavailable full texts. The reference lists of included articles were checked for relevant articles not identified by the initial search.

Extracted study characteristics included: study design, number of participants, rosacea symptoms, β-blocker type, dose, and treatment duration, erythema/flushing assessment method, study findings, and adverse events. A narrative synthesis was conducted for each β-blocker separately. Risk of bias was assessed by two reviewers (JGML and JIO), with disagreements resolved by discussion. The Cochrane Risk of Bias tool was used for assessment of risk of bias in randomized controlled trials (RCTs), with studies graded as having low, high, or unclear risk of bias.[35] For case-control studies, the Newcastle-Ottawa Scale was used.[36] For cohort studies without a control group (including case reports and case series), the Quality in Prognosis Studies (QUIPS) tool was used.[37] For the QUIPS, the overall risk of bias for each of the studies was judged as: (1) low, if there were a low

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risk of bias in all key domains, (2) unclear, if there were an unclear risk of bias for one or more key domains, and (3) high, if there were a high risk of bias for one or more key domains.

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Results

In total, 1941 articles were identified (Fig. 1). After duplicate removal, 1544 articles were screened, resulting in inclusion of 25 abstracts, eligible for full-text screening. Finally, nine articles were included in this systematic review. Investigated β-blockers were carvedilol (*n*=4),[26,38-40] propranolol (*n*=3),[29,41,42] nadolol (*n*=1),[30] and β-blockers in general (*n*=1).[43] Among included articles, there were one RCT, one cohort study, one case-control study, three case reports, and three case series. Below and in Table 1 and 2, the β-blockers included in this review are presented separately.

Nadolol

Nadolol is a nonselective β-blocker, blocking both β_1 and β_2-adrenergic receptors. Its use was described in one RCT.[30]

Fifteen rosacea patients with erythema and flushing received nadolol 40 mg once daily, twice daily, or placebo during 53 days. During this period, flushing challenges using warm water, ethanol, and nicotinic acid were performed. Intensity of flushing reactions was measured as degree of skin perfusion, using laser Doppler velocimetry. No statistically significant differences in skin perfusion index were seen between nadolol and placebo. A modest-significant subjective improvement in number, duration and intensity of flushing with nadolol was found in 60% of patients; however, slight-definite worsening of flushing with nadolol was seen in 13% of patients as well.

Carvedilol

Carvedilol is a nonselective β-blocker with additional weak α_1-blocking activity. Four publications describing use of carvedilol in rosacea were identified.[26,38-40]

In a retrospective case study, five patients with moderate-severe rosacea-associated flushing or persistent erythema were treated with carvedilol titrated up to 12.5 mg twice daily for ≥6 months.[39] All patients observed a reduction in facial erythema after 2-7 days since start of treatment,

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and clinical erythema scores decreased in all patients at ≥6 months treatment. Erythema and facial flushing were still provoked by known triggers, but to a much lower degree.

In another case series, carvedilol (3.125-6.25 mg, 2-3 times daily) was added to the regular medication (doxycycline, oral antihistamines/corticosteroids) of 11 patients with persistent erythema and facial flushing, and the dose was gradually titrated up to 31.25 mg/day.[26] This resulted in significant clinical erythema improvement within three weeks (range 3-21 days) since start of carvedilol, together with reduced cheek temperature, and a large patient's assessed symptom reduction. Moreover, carvedilol allowed concurrent medications to be decreased in dosage or stopped.

Additionally, carvedilol usage was described in two case reports.[38,40] Clinical and patient-assessed improvement in erythema and flushing was seen within two weeks carvedilol treatment of 6.25 mg 2-3 times daily, with increased improvement thereafter using maintenance therapy of 6.25 mg 1-3 times daily for 23 months. Moreover, only 6.25 mg daily was needed in summertime.[38] Lee et al showed clinical reduction of erythema and flushing after start of carvedilol (6.25-12/5 mg thrice daily) together with brimonidine gel. Dermatoscopy showed polygonal vessel disappearance and blood vessel vasoconstriction after months. Carvedilol was only needed intermittently afterwards during summer.[40]

Propranolol

Propranolol is a traditional, nonselective β-blocker; three studies focused on its use in rosacea.[29,41,42]

In a retrospective cohort study, nine patients with facial erythema and flushing received propranolol 10 mg 3 times daily with doses increased as tolerated until symptoms improved, which appeared to be 20-40 mg 2-3 times daily.[29] Eight patients reported diminished symptoms and fewer flushing episodes while taking propranolol (duration of onset not described); one patient did not experience improvement, but only received 100 mg thrice daily during one month without side effects, and elected to discontinue propranolol thereafter.

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Park et al studied treatment with propranolol 10 mg thrice daily during 12 weeks in 22 patients with papulopustular and erythematotelangiectatic rosacea, and compared this with doxycycline (*n*=15) and doxycycline and propranolol combination therapy (*n*=26).[42] The propranolol group showed a significant faster and larger reduction in clinical flushing scores compared to the other groups.

Lastly, erythema and flushing improvement was observed in one patient already after one week of treatment with propranolol 40 mg once daily combined with minocycline and tranexamic acid.[41]

β-blockers in general

One study evaluated the association of β-blockers and the risk of developing rosacea by performing a case-control study with 53.927 rosacea cases and 53.927 controls.[43] The paper does not describe which β-blocker types were included. A marginal decreased risk (OR 0.91, 95% CI 0.86-0.95) for current and long-term users of all β-blockers (OR 0.89, 95% CI 0.82-0.96) was found. Sensitivity analysis of the three most prescribed β-blockers in the United Kingdom (propranolol, atenolol, and bisoprolol) revealed that the risk was slightly decreased for current users of atenolol (OR 0.83, 95% CI 0.74-0.94), and for current long-term users of bisoprolol (OR 0.76, 95% CI 0.60-0.96). Unexpectedly, no decreased risk for developing rosacea among propranolol users was found.

Adverse events

Seven included studies reported about adverse event occurrence (Table 2).[26,29,30,38,39,41,42] For nadolol, decreased heart rate and blood pressure was seen in 100% and 93% of patients, respectively.[30] For carvedilol, treatment was discontinued in 9.1% of patients (1 in 11) due to hypotension,[26] and dosage was adjusted in 20% of patients (1 in 5) because of vertigo and nausea.[39] Additionally, feeling of weakness (1 in 5)[39] and decreased blood pressure (1 in 11)[38] were noticed during carvedilol treatment. For propranolol, treatment was discontinued in 22% of patients (2 in 9) due to dizziness,

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bradycardia, and balance loss sensation.[29] Other reported, acceptable, side effects were decreased migraine headache severity (2 in 9), weight gain (1 in 9), fatigue (1 in 9), dyspepsia (1 in 22), and headache (1 in 22).[29,42] The case report from Kwon reported no adverse events during treatment with propranolol.[41]

Risk of bias

The number of patients of most studies was small, including multiple case series/case reports. Although the RCT was double-blinded, no information about the allocation sequence and blinding procedure was given (Suppl. Fig. 1). In the case-control study, results could be biased by the co-presence of papules and pustules, and not solely erythema and flushing. For cohort studies, which were mostly retrospective, the domains 'Outcome measurement' and 'Study confounding' carried the highest risk of bias (Suppl. Fig. 2). It was often not stated how and by whom the outcome measurements were determined. Moreover, potential confounders such as comedication, rosacea type, cutaneous comorbidity, and rosacea-aggravating triggers were often insufficiently described or not taken into account.

Conclusions

Diminishing erythema and flushing in rosacea is challenging, since it hardly responds to conventional anti-inflammatory treatment. Patients in the included studies often had an extensive history of ineffective topical, oral and/or physical treatments. Most studies showed improved erythema and flushing after initiation of oral β-blockers. The evidence was highest for carvedilol and propranolol, two non-selective β-blockers. Unfortunately, only a small selection of available β-blocker types was examined.

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The most common adverse effects of non-selective β-blockers are bradycardia, hypotension, bronchospasm, dizziness, somnolence, and fatigue.[20,44] One should be aware that β-blockers may exacerbate asthma and psoriasis.[45-47] Contraindications to β-blockers are congestive heart failure, cardiogenic shock, sinus bradycardia <50 beats/min, atrioventricular block, hyperactive airway disease, and Raynaud's disease.[19] It is important to monitor patients for side effects, especially blood pressure and heart rate.[38]

Compared to other non-selective β-blockers, carvedilol and propranolol possibly have additional antioxidant and anti-inflammatory actions.[26,40,48,49] This may be beneficial in rosacea treatment, as reactive oxygen species released by inflammatory cells may play a role in disease development.[50-52] Carvedilol is usually well tolerated, even in elderly patients with heart failure.[53] Additionally, it results in less side effects like hypotension and bradycardia than traditional β-blockers, which may be a limiting factor in normotensive patients.[38,54] Propranolol can cause additional diarrhoea, nausea, and sexual dysfunction in males,[55] and it is recommended to start at a lower dosage in geriatric patients and patients with renal or hepatic disease.[20] Nadolol offers the advantage of a once-daily dosage due to its long plasma half-life (14-24h).[30] β-blockers dosages for reducing facial erythema are generally lower compared to the maintenance dose needed in hypertension (nadolol: 40-80 mg vs. 80-320 mg daily;[30] carvedilol: 6.25-37.5 mg vs. 25 mg daily;[26,38-40] propranolol: 30-120 mg vs. 160-320 mg daily[29,41,42]). The efficacy of topical β-blockers such as timolol, being effective in various vascular dermatoses,[20] has not been investigated in rosacea yet.

Several studies have investigated other systemic medications antagonising erythema and flushing in rosacea. Clonidine, an α_2-adrenergic agonist, did not suppress erythema and flushing.[56,57] Also rilmenidine, a central hypotensive drug, did not improve facial flushing compared to placebo.[58] Ondansetron, a serotonin antagonist, improved persistent erythema and flushing in two patients.[59] Naloxone, an opioid receptor antagonist, reduced alcohol-induced flushing, but has many side effects.[60] Otherwise, phentolamine, an α-adrenergic antagonist, even increased blood flow during

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exercise in frequent blushers.[28] Aforementioned medications therefore seem largely dissatisfying until today.

The quality of included studies was relatively low, and interstudy outcome variability was large. It was not possible to perform a meta-analysis, because erythema and flushing were assessed using a wide spectrum of mostly subjective clinical and patient-based scores, and method standardization was often missing. Evaluation of facial erythema by visual assessment alone lacks objectivity and precision, and is prone to inter- and intra-observer variability.[61-63] This makes comparison of individual study outcomes challenging. Simple, standardized, and objective erythema and flushing assessment, such as spectrophotometry and computer-aided image analysis, are advisable.[64]

To conclude, oral non-selective β-blockers could be an effective treatment option for rosacea patients with persistent facial erythema and flushing. Currently, most evidence is available for carvedilol and propranolol. Large, prospective, clinical trials are warranted to validate the data of these small studies. Researchers should further focus on determination of the optimal dosage, treatment duration, and long-term therapeutic effects for adequate treatment of erythema and flushing in rosacea.

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Figure legend

Figure 1. Flow chart: article selection process.

Supplemental figure 1. Review author's judgement about each risk of bias item for the included RCT (*n*=1) with the Cochrane Risk of Bias tool.

Supplemental Figure 2A. Review author's judgement about each risk of bias item for each included cohort study and case report/series (*n*=7) with the Quality in Prognosis Studies tool.

Supplemental Figure 2B. Review author's judgement about each risk of bias item presented as percentages across all included cohort studies and case reports/series (*n*=7) with the Quality in Prognosis Studies tool.

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Table 1. Summary of included studies evaluating the efficacy of β-blockers in rosacea patients with flushing and persistent facial erythema.

Author	Study design	Participants, *n*	Rosacea symptoms	Treatment (type, dose, duration)	Erythema/flushing assessment	Study findings	AEs
Wilkin[30]	RCT	15 (F; 11, M: 4; age range 41-60 y)	ETR with flushing, erythema, telangiectasia	Study periods: A=18 days, B=17 days, C=18 days). Four groups: 1 (*n*=4): A+B=placebo, C=nadolol 40 mg QD; 2 (*n*=3): A+B=placebo, C=nadolol 40 mg BID; 3 (*n*=4): A=nadolol 40 mg QD, B+C=placebo; 4 (*n*=4): A=nadolol 40 mg BID, B+C=placebo. Flushing challenges: water (60 °C), ethanol, nicotinic acid at day 14+18 of period A+C.	RR, heart rate, laser Doppler velocimetry at right malar area for skin perfusion, patient's perception (flushing number, duration, intensity)	No statistically significant differences in perfusion index values between nadolol and placebo during flushing challenges. Modest to significant subjective improvement on spontaneous flushing with nadolol in 9 of 15 patients; slight to definite worsening of spontaneous flushing with nadolol in 2 of 15 patients.	Lower heart rate with nadolol (61±2.5/min) than placebo (70±2.5/min) in all patients. Lower mean arterial pressure with nadolol (76±2.5mmHg) than placebo (80±2.5mmHg) in 14 of 15 patients.
Pietschke and Schaller[39]	Retrospective case study	5 (F: 3, M: 2; age range 26-59 y)	Severe frequent flushing or persistent erythema	Carvedilol titrated up to 12.5 mg BID ≥ 6 months	Clinicians erythema assessment (CEA), patient's assessment (patients self-assessment (PSA), level of satisfaction, level of embarrassment)	All patients observed reduced facial erythema after 2-7 days of treatment. Mean CEA decreased from 3.4 at baseline to 0.4 after ≥6 months of treatment. Mean PSA decreased from 3.8 at baseline to 0.8 after ≥6 months of treatment. All 5 patients satisfied or highly satisfied with impact of carvedilol, with decreased level of embarrassment (3.4 to 0 after ≥6 months).	Vertigo and nausea (*n*=1), feeling of weakness (*n*=1)
Hsu and Lee[26]	Case series	11 (F:9, M; 2; age range 17-47 y)	Facial erythema	Carvedilol 3.125-6.25 mg BID or TID, titrated up to 31.25 mg/day, for 1 wk-28 months	Clinical photographs, cheek temperature, patients' assessment (VAS)	Significant clinical improvement within 3 weeks (range 3-21 days, mean 10.5 days), mean reduction of cheek temperature with 2.2°C, mean reduction of 6.3 on VAS scale	Hypotension (*n*=1)
Hsu and Lee[38]	Case report	1 (F, 48 y)	Flushing, persistent erythema, telangiectasia	Carvedilol (6.25 mg BID) for 1 week, then 6.25 mg QD, BID or TID for 23 months	Clinical (not further specified), cheek temperature, patients' assessment (VAS), RR	Dramatic improvement in erythema and telangiectasia within 2 weeks of treatment. Continuation of improvement with minimal erythema and only transient flushing episodes thereafter. Reduction in cheek temperature from 36.9°C to 30.0°C. Mean VAS reduction from 10 to 1.	Reduction in RR from 130/70 to 110/60 mmHg. No bradycardia.
Lee and Lee[40]	Case report	1 (F, 59 y)	ETR with transient and persistent erythema, telangiectasia	Carvedilol (6.25-12.5 mg TID; duration ND) and topical 0.33% brimonidine daily	Clinical (not further specified), dermoscopy	*Clinical:* persistent erythema resolved in 3 weeks after starting brimonidine. Only minimal telangiectasia at 6-month follow-up. Only mild flares over the 11 months. *Dermoscopy:* disappearance of polygonal vessels and significant vasoconstriction of	ND

						larger blood vessels after months.	
Kwon et al[41]	Case report	1 (F, 37 y)	Flushing, persistent erythema, and marked telangiectasia	Propranolol (40 mg QD), minocycline (50 mg QD), and tranexamic acid (250 mg QD) for 1 month	Clinical (not further specified)	Noticeable improvement of erythema and subjective symptoms already after 1 week of treatment, persisting for 2 months.	No AE
Park et al[42]	Prospective cohort study	63 (F: 47, M: 16; age range 16-76 y)	ETR or PPR with flushing	Propranolol 10 mg 3 TID (*n*=22), doxycycline 100 mg BID (*n*=15), propranolol 10 mg BID+doxycycline 100 mg BID (*n*=26). Duration: 12 weeks.	Investigator Global Assessment (IGA), rosacea clinical score (ARCS), Patient Global Assessment (PGA)	Decrease of IGA, ARCS and PGA in all three groups with no statistically significant differences. Propranolol group: flushing scores showed the biggest and fastest decrease after 12-week treatment compared to the other groups (statistically significant).	Propranolol-related: dyspepsia and headache (*n*=1)
Craige and Cohen[29]	Retrospective cohort study	9 (F; 8, M: 1; age range 31-69 y)	Facial erythema, flushing	Propranolol (10 mg TID) with doses increased as tolerated until symptoms improved	Patient's perception (flushing episodes, symptoms, quality of life)	8 of 9 patients: diminished symptoms and flushing episodes. None had sufficient relief from 10 mg TID. Dose needed to control flushing: 20-40 mg BID or TID. 1 patient: no improved flushing, only received 10 mg TID for one month, elected to discontinue thereafter.	Bradycardia, fatigue, dizziness (*n*=1), dizziness and sensation of balance loss (*n*=1), mild weight gain (*n*=1), decreased migraine headache severity (*n*=2)
Spoendlin et al[43]	Case-control study	53.927 cases, 53.927 controls	Rosacea (PPR and ETR)	β-blockers in general	ND	Slightly decreased OR in current (OR=0.91) and long-term β-blocker users (OR=0.89). Slightly decreased OR during current use of atenolol across all strata of exposure duration (OR 0.74-0.83) and long-term current use of bisoprolol (OR 0.76). No decreased OR for propranolol use.	ND

AEs, adverse events; BID, twice daily; ETR, erythematotelangiectatic rosacea; F, female; M, male; OR, odds ratio; ND, not described; PPR, papulopustular rosacea; QD, once daily; RR, blood pressure; TID, thrice daily

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Table 2. Reported adverse events in rosacea patients treated with oral β-blockers for flushing and persistent facial erythema.

Treatment	Reported adverse events
Nadolol	Decreased heart rate (*n*=15)[30]; decreased blood pressure (*n*=14)[30]
Carvedilol	Hypotension (*n*=1)[26]; decreased blood pressure (*n*=1)[38]; vertigo and nausea (*n*=1)[39]; feeling of weakness (*n*=1)[39]
Propranolol	Dizziness (*n*=2)[29]; decreased migraine headache severity (*n*=2)[29]; dyspepsia (n=1)[42]; headache (*n*=1)[42]; bradycardia (*n*=1)[29]; sensation of balance loss (*n*=1)[29]; weight gain (n=1)[29]; fatigue (*n*=1)[29]

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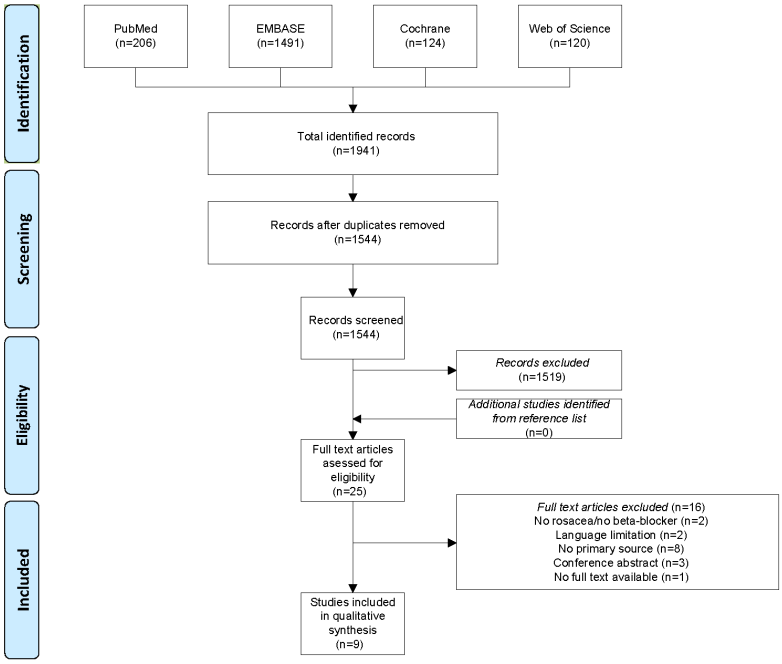
Identification
Screening
Eligibility
Included
PubMed (n=206)
EMBASE (n=1491)
Cochrane (n=124)
Web of Science (n=120)
Total identified records (n=1941)
Records after duplicates removed (n=1544)
Records screened (n=1544)
Records excluded (n=1519)
Additional studies identified from reference list (n=0)
Full text articles asessed for eligibility (n=25)
Full text articles excluded (n=16)
No rosacea/no beta-blocker (n=2)
Language limitation (n=2)
No primary source (n=8)
Conference abstract (n=3)
No full text available (n=1)
Studies included in qualitative synthesis (n=9)