



Strategies and Adjunctive Therapies for Proton Pump Inhibitor Deprescribing: A Comprehensive Literature Review of Withdrawal, Rebound Acid Hypersecretion, Rescue Therapy, and Complementary Approaches

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Abstract

Background: Proton pump inhibitors (PPIs) are frequently continued for prolonged periods despite initially time-limited indications. Discontinuation may be complicated by recurrent symptoms and rebound acid hypersecretion (RAHS), potentially contributing to unnecessary long-term treatment. Although several deprescribing strategies have been investigated, the optimal withdrawal approach and the role of adjunctive therapies remain uncertain.

Objective: To comprehensively review strategies for reducing or discontinuing PPI therapy and to examine pharmacological, non-pharmacological, herbal, and complementary interventions that may help control symptoms during withdrawal.

Methods: A broad narrative literature search was conducted across major biomedical databases and complementary/traditional medicine sources. Evidence was organized into three pragmatic categories: direct PPI deprescribing evidence, potential bridge-therapy evidence for gastroesophageal reflux disease (GERD), and exploratory or substantially indirect evidence.

Results: Direct evidence supports several approaches to reducing PPI exposure, including abrupt withdrawal, gradual tapering, dose or frequency reduction, on-demand treatment, H₂-receptor antagonist (H₂RA) rescue, alginate rescue, structured education, weight reduction, and potentially diaphragmatic breathing. Direct comparisons have not established clear superiority of tapering over abrupt discontinuation for sustained cessation, although tapering may reduce symptom burden. Alginates and H₂RAs have the most directly applicable evidence for symptom control during withdrawal. Several complementary interventions, including *Monteverdia ilicifolia*, standardized *Glycyrrhiza glabra*, *Aloe vera*, melatonin, acupuncture, and selected Chinese herbal formulations, have clinical evidence for GERD symptom control but lack direct evidence that they improve PPI withdrawal success.

Conclusions: PPI deprescribing is feasible in appropriately selected patients, but no single withdrawal protocol has been established as optimal. Management of transient symptoms and underlying reflux mechanisms may be as important as the method of PPI reduction. Bridge and rescue therapies represent an important and insufficiently studied component of deprescribing.

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Keywords: proton pump inhibitors, deprescribing, discontinuation, rebound acid hypersecretion, gastroesophageal reflux disease, alginate, H₂-receptor antagonists, complementary medicine, herbal medicine

Introduction

Proton pump inhibitors (PPIs) are among the most commonly used medications for acid-mediated upper gastrointestinal disorders. They are highly effective for gastroesophageal reflux disease (GERD), peptic ulcer disease, selected gastroprotection indications, and as components of *Helicobacter pylori* eradication regimens. However, treatment that begins for a time-limited

indication is often continued without systematic reassessment. Contemporary expert guidance therefore emphasizes periodic review of the indication and consideration of dose reduction or discontinuation when a continuing evidence-based indication is absent ^[1, 2].

Deprescribing can include complete cessation, reduction to the lowest effective dose, reduction in dosing frequency, step-down to a less potent acid-suppressive strategy, or conversion to intermittent or on-demand treatment. Importantly, deprescribing should not be undertaken indiscriminately in patients with clear indications for chronic acid suppression, including selected patients with complicated GERD or substantial upper gastrointestinal bleeding risk ^[1, 2].

One barrier to withdrawal is rebound acid hypersecretion (RAHS). In a randomized double-blind trial of 120 healthy volunteers, 44% of participants exposed to esomeprazole developed clinically relevant acid-related symptoms after withdrawal compared with 15% receiving placebo ^[3]. A subsequent review confirmed that rebound symptoms can occur in previously asymptomatic volunteers, while emphasizing that their frequency and clinical importance in patients with established reflux disease remain uncertain ^[4].

This phenomenon may create a self-perpetuating clinical cycle in which symptoms appearing shortly after withdrawal are interpreted as recurrence of the original disorder, prompting rapid resumption of PPI therapy. Successful deprescribing may therefore depend not only on the withdrawal schedule but also on education, symptom rescue, and correction of modifiable mechanisms contributing to reflux.

Recent evidence syntheses demonstrate that PPI deprescribing has been approached through a wide range of interventions, including tapering, abrupt cessation, on-demand treatment, pharmacist- or clinician-led medication review, education, and multidisciplinary programs. Nevertheless, considerable heterogeneity remains, and the optimal method of withdrawal is unresolved ^[5]. The present comprehensive literature review therefore examines both established deprescribing strategies and potential adjunctive approaches that might function as temporary bridge therapies during withdrawal, including pharmacological rescue, lifestyle and behavioral interventions, herbal medicines, and selected traditional medical approaches.

Methods

This article was developed as a comprehensive narrative literature review rather than a systematic review. The literature search and presentation were structured to maximize transparency, clinical relevance, and balanced discussion in accordance with principles proposed for high-quality narrative reviews, including explicit description of the search approach and clear differentiation between direct and

indirect evidence ^[6].

Searches were conducted across MEDLINE/PubMed and complementary searches of Embase-, Scopus-, Web of Science-, Cochrane-, CINAHL-, LILACS-, SciELO-, Google Scholar-, Chinese- and Indian/traditional-medicine-indexed literature when accessible through searchable sources and secondary evidence maps. Reference lists of relevant guidelines, reviews, and primary studies were also examined. Search concepts included proton pump inhibitor, PPI, deprescribing, withdrawal, discontinuation, cessation, tapering, dose reduction, step-down, on-demand, rebound acid hypersecretion, rescue therapy, bridge therapy, alginate, H2-receptor antagonist, weight loss, diaphragmatic breathing, acupuncture, melatonin, Aloe vera, Glycyrrhiza, deglycyrrhized licorice, *Maytenus ilicifolia*, *Monteverdia ilicifolia*, Chinese herbal medicine, Ayurveda, probiotics, psyllium, ginger, curcumin, and related terms.

Priority was given to randomized controlled trials, prospective interventional studies, comparative clinical studies, major guidelines, and evidence syntheses useful for locating primary studies. Evidence was organized into three clinically pragmatic groups: (1) direct deprescribing evidence, in which PPI cessation, dose reduction, dosing-frequency reduction, on-demand conversion, or PPI consumption was explicitly measured; (2) potential bridge-therapy evidence, in which an intervention demonstrated clinical activity against GERD symptoms but was not specifically tested for successful PPI withdrawal; and (3) exploratory evidence, including substantially indirect populations, small uncontrolled studies, heterogeneous traditional formulations, or evidence insufficient to support a withdrawal-specific inference.

No PRISMA flow diagram, formal systematic-review study count, meta-analysis, or claim of exhaustive study capture was used because the article was designed as a broad literature review. Quantitative findings are reported only when they could be traced to the cited source.

Results

1. Direct Strategies for PPI Reduction and Discontinuation

Direct evidence indicates that successful PPI reduction can be achieved through several pathways rather than a single standardized withdrawal regimen (Table 1). In a randomized open-label trial of 38 patients with GERD, Hendricks *et al.* compared abrupt cessation with tapering. At 12 months, there was no significant difference between strategies in sustained discontinuation, but the taper group reported less symptom burden at several follow-up points. H2RA use was associated with a 79% reduction in the risk of failure to discontinue PPI ($p=0.004$), suggesting that rescue therapy may influence success at least as much as the precise withdrawal schedule ^[7].

Table 1: Clinical evidence directly related to proton pump inhibitor deprescribing or reduction.

Study	Design / population	Intervention	Key findings	Interpretation
Hendricks <i>et al.</i> [7]	Randomized open-label trial; 38 randomized GERD patients	Abrupt cessation vs taper; H2RA permitted	No significant 12-month difference in discontinuation; taper had fewer symptoms at several time points; H2RA use associated with 79% lower failure risk	Direct withdrawal evidence
Coyle <i>et al.</i> [8]	Prospective primary-care intervention; 6,249 eligible long-term users	Education + individualized reduction/cessation + alginate rescue	75.1% stepped down/off at 12 months; 40.3% stopped completely; 8.7% returned to original dose	Direct deprescribing/rescue evidence
Vales <i>et al.</i> [9]	Randomized washout trial; 48 evaluable patients	Structured alginate QID during 1-week PPI washout vs standard instructions	Symptoms increased in controls but not significantly in alginate group	Direct short-term withdrawal symptom evidence
Kang <i>et al.</i> [10]	Systematic review/meta-analysis; 11 RCTs, 6,138 GERD patients	On-demand vs continuous PPI	Similar failure overall, especially NERD/mild ERD; substantially lower PPI exposure with on-demand therapy	Direct exposure-reduction evidence
de Bortoli <i>et al.</i> [11]	Comparative study; overweight/obese GERD	Structured weight loss + PPI vs standard diet + PPI	27/50 discontinued PPI; 16/50 halved dose; no complete discontinuation in standard-diet group	Direct non-pharmacological reduction evidence
Sadiq <i>et al.</i> [12]	Randomized trial; 22 GERD patients	Abdominal breathing + on-demand dexlansoprazole vs on-demand PPI alone	Mean PPI use 0.72 vs 4.63 doses over 4 weeks	Preliminary direct PPI-use reduction evidence

Alginate therapy has particularly relevant withdrawal-specific evidence. In a prospective intervention involving 6,249 eligible long-term PPI users, a program combining education, an individualized plan to reduce or stop therapy, and alginate rescue resulted in 75.1% of patients stepping down or off PPIs at 12 months; 40.3% discontinued PPIs completely and only 8.7% returned to their original dose [8]. In a randomized pre-investigation washout trial, symptom burden increased significantly in controls after PPI cessation but did not significantly increase among patients receiving structured alginate four times daily, although this trial evaluated only a one-week washout period [9].

On-demand treatment represents another evidence-supported method of reducing cumulative exposure. A meta-analysis of 11 randomized studies including 6,138 patients found broadly similar treatment-failure outcomes between on-demand and continuous therapy overall, particularly in non-erosive or mild erosive disease, while reducing PPI consumption substantially. Continuous maintenance remained more appropriate in populations with more severe erosive disease [10].

Interventions directed at reflux mechanisms may also reduce

medication requirements. In overweight or obese patients with GERD, a structured weight-loss program was associated with complete PPI discontinuation in 27 of 50 patients and halving of the dose in another 16 of 50; none of 51 patients receiving standard dietary advice discontinued PPI because of recurrent symptoms [11]. A small randomized trial of abdominal breathing exercises found markedly lower on-demand dexlansoprazole consumption over four weeks (mean 0.72 versus 4.63 doses), providing preliminary evidence that diaphragmatic training may reduce PPI requirements [12].

2. Adjunctive and Complementary Interventions Potentially Applicable as Bridge Therapies

A second body of literature concerns interventions that improve GERD symptoms but have not been directly tested as facilitators of PPI withdrawal (Table 2). These studies are clinically relevant because temporary symptom control during the withdrawal period could theoretically reduce reflexive PPI resumption, but efficacy for GERD should not be equated with proven deprescribing efficacy.

Table 2: Adjunctive and complementary interventions with potential application as bridge therapies during PPI withdrawal.

Intervention / study	Design / N	Regimen / comparator	Main clinical finding	Relationship to PPI withdrawal
Monteverdia ilicifolia (espinheira-santa) [13]	Randomized double-blind double-dummy; n=86	400 mg or 860 mg vs omeprazole 20 mg; 4 weeks	All groups improved GERD symptom and heartburn-QoL scores	Indirect; GERD treatment, not withdrawal
Low-glycyrrhizin Glycyrrhiza glabra (GutGard) [14]	Phase III randomized double-blind placebo-controlled; n=200	Standardized extract vs placebo; 28 days	Better GERD-related QoL and earlier heartburn/regurgitation improvement	Indirect bridge candidate
Aloe vera [15]	Pilot randomized positive-controlled; n=79	Aloe syrup vs omeprazole vs ranitidine; 4 weeks	Reduced frequency of assessed GERD symptoms	Indirect bridge candidate
Melatonin [16]	Randomized double-blind; n=78	Melatonin 3 mg + omeprazole 20 mg vs omeprazole + placebo; 4 weeks	Greater improvement in heartburn, epigastric pain and FSSG	Indirect add-on/bridge candidate
Wu Chu Yu Tang [17]	Randomized double-blind; n=90	WCYT 3 g TID vs omeprazole 20 mg; 4 weeks	Both improved RDQ/GERDQ; reported longer persistence after WCYT	Indirect bridge candidate
Chinese herbal medicine evidence map [18]	Systematic review/network meta-analysis; 20 RCTs, n=2,246	Multiple standardized and non-standardized formulations vs biomedical treatment	Signals of symptom efficacy and recurrence benefit; substantial heterogeneity	Indirect; useful for selecting future bridge candidates

Monteverdia ilicifolia (formerly Maytenus ilicifolia; espinheira-santa) was evaluated in a randomized, double-blind, double-dummy clinical trial involving 86 patients with GERD symptoms. Participants received omeprazole 20 mg, M. ilicifolia 400 mg, or M. ilicifolia 860 mg for four weeks. All groups showed significant improvement in GERD symptom and heartburn-related quality-of-life scores, without significant differences in the principal post-treatment outcomes [13].

A standardized flavonoid-rich, low-glycyrrhizin Glycyrrhiza glabra extract was evaluated in a phase III double-blind placebo-controlled trial of 200 participants. The active-treatment group demonstrated better GERD-related quality of life and earlier improvement in heartburn and regurgitation than placebo [14]. Aloe vera syrup was evaluated in a randomized positive-controlled pilot trial of 79 participants and reduced the frequency of assessed GERD symptoms during four weeks of treatment [15]. Melatonin 3 mg added to omeprazole 20 mg was superior to omeprazole plus placebo for several symptom outcomes in a randomized double-blind trial of 78 patients [16].

Traditional Chinese medicine provides another substantial

body of GERD research. Wu Chu Yu Tang was compared with omeprazole in a randomized double-blind trial of 90 patients; both treatments improved validated reflux scores during therapy, and the herbal-treatment effect appeared to persist longer after treatment in the reported follow-up [17]. A 2026 evidence synthesis incorporating English and Chinese databases identified 20 randomized trials involving 2,246 patients and multiple Chinese herbal formulations, while also demonstrating substantial heterogeneity in formulations and study characteristics [18]. These findings support further investigation of selected standardized formulations but do not demonstrate successful PPI withdrawal.

3. Exploratory and Indirect Interventions

Additional interventions were considered too indirect or methodologically limited for inclusion among the principal bridge-therapy candidates (Table 3). A systematic review of probiotics identified 13 prospective studies, with 11 reporting benefit for at least one GERD-related outcome; however, strains, doses, populations, and endpoints were heterogeneous, and PPI withdrawal was not established as an outcome [19].

Table 3: Exploratory interventions with indirect or insufficient evidence for application to PPI deprescribing.

Intervention	Evidence	Main finding	Why evidence is indirect / insufficient
Probiotics [19]	Systematic review; 13 prospective studies	11/13 reported benefit for at least one GERD-related outcome	Marked heterogeneity; no demonstrated PPI-withdrawal effect
Baladi Manduram (Ayurveda) [20]	Non-randomized single-arm open-label study; n=30	Symptomatic improvement in Amlapitta	No control group; traditional diagnostic construct; no withdrawal endpoint
Curcuma longa [21]	Randomized double-blind placebo-controlled; n=132	Improved functional dyspepsia; several outcomes similar to omeprazole	Functional dyspepsia, not GERD; no withdrawal endpoint
Other nutraceutical/dietary combinations	Small heterogeneous clinical literature	Possible symptom benefit reported for selected preparations	Variable ingredients, populations and endpoints; insufficient direct evidence
Lemon / Citrus limon / lemon water	No adequate controlled human withdrawal trial identified	No reliable efficacy estimate	Anecdotal/traditional use only for this question; should not be presented as evidence-based PPI deprescribing

Evidence from Ayurveda was substantially weaker. Baladi Manduram was evaluated in a non-randomized, single-arm, open-label study of 30 patients with Amlapitta, a traditional diagnostic construct with GERD-like symptoms. Symptomatic improvement was reported, but the uncontrolled design and diagnostic differences make application to PPI deprescribing highly uncertain [20].

Curcumin provides another example of evidence that is clinically interesting but too indirect for the main GERD bridge-therapy table. In a randomized double-blind placebo-controlled trial of 132 patients with Rome IV functional dyspepsia, Curcuma longa improved symptoms and was not significantly different from omeprazole for several outcomes; however, functional dyspepsia is not equivalent to GERD, and no PPI-withdrawal question was tested [21].

No adequate controlled human evidence was identified supporting lemon or lemon-water consumption as a strategy for preventing RAHS or facilitating PPI discontinuation. Anecdotal or traditional use was therefore not treated as evidence of efficacy.

Discussion

This review suggests that PPI deprescribing is better conceptualized as a structured transition than as a binary decision to continue or stop therapy. The evidence supports three interrelated clinical tasks: confirming that long-term acid suppression is no longer required, selecting a practical

reduction strategy, and controlling symptoms during the transition. Earlier literature reviews already demonstrated that PPI discontinuation is feasible but that withdrawal regimens vary substantially [22].

Direct randomized evidence does not establish that tapering is superior to abrupt cessation for long-term success [7]. Nevertheless, tapering may reduce symptom burden, and this distinction is clinically relevant. A patient who experiences less heartburn or dyspepsia during withdrawal may be less likely to interpret transient symptoms as proof of permanent PPI dependence. Current expert guidance accordingly permits either tapering or abrupt discontinuation in appropriate candidates [1].

RAHS provides a plausible physiological explanation for at least part of the early symptom burden after withdrawal. The randomized volunteer study by Reimer *et al.* demonstrated that PPI exposure can itself be followed by acid-related symptoms after treatment stops [3]. However, the clinical importance of symptomatic rebound in established GERD is less certain [4]. Thus, recurrent symptoms after discontinuation may represent RAHS, recurrence of the underlying disorder, or both. The distinction is important because immediate resumption of long-term PPI therapy may be unnecessary in some patients.

One of the most clinically useful observations is the potential importance of rescue therapy. In the Hendricks trial, H2RA use was associated with a substantially lower risk of failed

discontinuation [7]. Alginate evidence is particularly compelling because it includes both a large real-world deprescribing intervention [8] and randomized washout data showing prevention of symptom exacerbation [9]. These studies support a shift from asking only 'taper or stop?' toward asking how the withdrawal period can be made tolerable. Complete cessation should also not be the only definition of success. On-demand treatment can substantially reduce cumulative exposure while maintaining symptom control in selected patients [10]. Similarly, reduction from twice-daily to once-daily treatment or use of the lowest effective dose may represent clinically meaningful deprescribing. Patients with complicated GERD, Barrett's esophagus in relevant contexts, or substantial upper gastrointestinal bleeding risk require a different approach and should not undergo indiscriminate withdrawal [1, 2].

Weight reduction is particularly important because it targets reflux mechanisms rather than simply replacing one acid-suppressive medication with another. The large reduction in PPI requirements observed after successful weight loss [11] supports incorporating weight management when clinically appropriate. Abdominal or diaphragmatic breathing is another mechanistically attractive approach because the crural diaphragm contributes to the antireflux barrier; the preliminary reduction in on-demand PPI use warrants confirmation in larger trials [12].

The complementary-therapy literature raises a different question: can a treatment with demonstrated GERD symptom activity serve temporarily as a bridge while a PPI is withdrawn? Espinheira-santa [13], standardized low-glycyrrhizin licorice [14], Aloe vera [15], melatonin [16], and Wu Chu Yu Tang [17] all have human clinical data, but none of these trials was designed to determine whether the intervention increases sustained PPI discontinuation. Their correct interpretation is therefore 'potential bridge therapy,' not established deprescribing treatment.

The Chinese literature is especially important because conventional English-language searching can underrepresent this evidence base. The recent synthesis of 20 randomized trials [18] suggests that several standardized formulations deserve closer examination. However, heterogeneity in botanical composition, comparators, outcome definitions, and methodological quality argues against treating 'Chinese herbal medicine' as a single intervention. Future withdrawal trials should select reproducible formulations and use sustained PPI discontinuation as an explicit endpoint.

Exploratory interventions should remain clearly separated from stronger evidence. Probiotic studies are heterogeneous [19]; Ayurvedic evidence such as Baladi Manduram is currently uncontrolled [20]; and curcumin evidence derives from functional dyspepsia rather than GERD [21]. This hierarchical presentation is important because a positive symptom trial in another gastrointestinal disorder cannot establish efficacy for PPI withdrawal.

A useful future trial would randomize long-term PPI users without a mandatory maintenance indication to a standardized withdrawal strategy and then independently randomize them to a bridge intervention or usual rescue care. Sustained PPI discontinuation at 8-12 weeks and again at 6-12 months should be primary clinical endpoints, accompanied by cumulative PPI exposure, symptom burden,

rescue-medication consumption, quality of life, and adverse events. The protocol study by Hojo *et al.*, which compares abrupt cessation with a two-week half-dose taper, illustrates the continued interest in defining a reproducible withdrawal strategy, although its publication describes the trial design rather than outcome data [23].

The principal strength of this review is its deliberately broad clinical perspective, integrating conventional deprescribing, rescue therapy, behavioral and lifestyle approaches, and complementary medicine while preserving a hierarchy between direct and indirect evidence. Its principal limitation is equally important: this is a comprehensive narrative review, not a systematic review. The search was broad but was not accompanied by duplicate screening, a PRISMA flow diagram, formal risk-of-bias assessment of every included study, or a claim of exhaustive capture. Accordingly, the tables should be interpreted as an evidence-oriented clinical map rather than a systematic-review evidence inventory.

Conclusion

PPI deprescribing is feasible in appropriately selected long-term users, but current evidence does not identify a single optimal withdrawal strategy. Tapering may improve tolerability, while abrupt cessation can also be successful. On-demand treatment, H2RA rescue, and particularly alginate rescue offer practical ways to reduce exposure or manage the withdrawal period. Weight reduction and possibly diaphragmatic breathing address mechanisms contributing to reflux and may further reduce PPI requirements.

Complementary interventions including *Monteverdia ilicifolia*, standardized *Glycyrrhiza glabra*, Aloe vera, melatonin, and selected Chinese herbal formulations have clinical evidence for GERD symptom control but have not yet been shown to facilitate sustained PPI withdrawal. Their most appropriate current role is as candidates for dedicated bridge-therapy trials. A structured approach combining reassessment of indication, individualized withdrawal, patient education, temporary symptom rescue, and correction of modifiable reflux mechanisms may be more clinically useful than medication cessation alone.

Declarations

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Conflicts of Interest

The author declares no conflicts of interest related to this work.

Data Availability Statement

All data discussed in this review were derived from previously published studies and publicly available sources. No original patient-level dataset was generated.

Ethics Approval

Ethics committee approval was not required because this article is a literature review of previously published data and did not involve collection of new data from human participants or animals.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Use of Artificial Intelligence and Language Assistance

The manuscript was initially written by the author in Portuguese and translated into English with the assistance of ChatGPT (OpenAI). ChatGPT was also used for language refinement, grammatical correction, organization, and editorial assistance. The author critically reviewed, verified, and revised the scientific content and assumes full responsibility for the accuracy, integrity, interpretation, and final content of the manuscript. Artificial intelligence was not considered an author.

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