



Therapeutics
Initiative
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**Comparative Analysis of the
Efficacy and Safety of
Various Single Enantiomer and
Racemic Mixture Pairs**

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Abstract

Introduction:

Chiral switching and single-isomer development have led to preferential prescribing of newer, pure isomer agents despite substantially higher costs. Dexlansoprazole, the R-(+)-enantiomer of lansoprazole, has recently surpassed its parent drug for acid-related gastrointestinal disorders. Escitalopram, the S-(+)-enantiomer of racemic citalopram, has similarly replaced citalopram in depression treatment. Esomeprazole, the S-(-)isomer of omeprazole, is widely promoted for claimed pharmacokinetic and therapeutic advantages. Although claims suggest these enantiomers are safer, more effective, faster acting, or provide superior clinical benefits, the clinical significance of these purported advantages remains uncertain.

Objective:

To examine utilization patterns in British Columbia (BC) and critically evaluate the comparative pharmacological profiles, clinical efficacy, safety, and cost-effectiveness of dexlansoprazole versus lansoprazole, escitalopram versus citalopram, and esomeprazole versus omeprazole, to determine whether claims supporting preferential prescribing are justified.

Methods:

Systematic and narrative reviews were conducted using MedLine, EMBASE, PubMed, Cochrane CENTRAL, Epistemonikos, regulatory sources, and product monographs. Searches were performed from inception through 2024/2025, depending on the drug class. Provincial prescribing data (2000–2024) were analyzed using PharmaNet and related administrative health databases to assess annual prevalence of use and trends. Head-to-head randomized controlled trials (RCTs) were included. Outcomes assessed included healing of erosive esophagitis (EE) and symptom resolution in gastroesophageal reflux disease (GERD) for dexlansoprazole-lansoprazole, antidepressant response and remission in major depressive disorder (MDD) for escitalopram-citalopram, bioavailability and acid suppression potency for esomeprazole-omeprazole, adverse drug reactions (ADRs), and economic considerations. Study robustness was evaluated using minimal clinically important differences, the Fragility Index, and the Cochrane Risk of Bias 2 Tool.

Results:

Across all three comparisons, newer enantiomers have become predominant in BC despite substantially higher costs. Dexlansoprazole prescriptions surpassed lansoprazole in 2024; escitalopram became the predominant antidepressant from 2013–2022 while citalopram use declined; and esomeprazole use exceeded omeprazole, influenced by formulary status and prescriber preference, and seen in the prescribing data year-over-year.

Twelve RCTs (N=2,552) compared escitalopram and citalopram in adults with MDD. All were at high risk of bias. No trial demonstrated a clinically meaningful advantage of escitalopram over citalopram. Reported differences favoring escitalopram did not exceed minimal clinically important differences, and claims of faster onset were inconsistent. ADRs were similar, with no evidence of differential QT prolongation or clinically meaningful safety advantages.

Four RCTs (N=4,584) compared dexlansoprazole and lansoprazole in adults with EE or GERD. Two reported the superiority of dexlansoprazole for specific outcomes; however, findings were fragile and overall study quality was low, with high risk of bias. Safety outcomes were comparable.

Multiple RCTs and pharmacodynamic studies compared esomeprazole and omeprazole. Esomeprazole demonstrated superior bioavailability and more consistent acid suppression, attributed to reduced interindividual variability. Clinical trials showed marginally higher healing rates in EE and modest improvements in GERD symptom control; however, differences were small, fragile, and often clinically insignificant. Omeprazole remained substantially less costly.

Across all comparisons, adverse events were similar between enantiomers and their parent drugs. Most included trials were at high risk of bias, and superiority findings were frequently fragile or methodologically limited.

Conclusion:

Preferential prescribing of dexlansoprazole, escitalopram, and esomeprazole in BC is not supported by robust head-to-head evidence demonstrating clinically meaningful superiority. Observed differences are modest, fragile, and methodologically limited, while cost differentials are substantial. Current utilization trends do not consistently align with the best available evidence and represent an opportunity for more cost-effective, evidence-based prescribing.

Introduction

Escitalopram / Citalopram

Citalopram is a racemic selective serotonin reuptake inhibitor (SSRI) comprising the S-(+)-enantiomer (S-citalopram) and the R-(-)-enantiomer (R-citalopram), whereas escitalopram consists solely of the S-enantiomer.

There are claims that escitalopram is safer, more effective, and faster-acting than citalopram for the treatment of major depressive disorder (MDD). However, escitalopram is approximately twice as expensive as citalopram, which raises questions about whether the single-enantiomer formulation provides clinically meaningful advantages over its racemic parent.

Dexlansoprazole / Lansoprazole

Lansoprazole is a proton pump inhibitor (PPI) composed of a 1:1 racemic mixture of the R-(+)- and S-(-)-enantiomers, whereas dexlansoprazole consists solely of the R-(+)-enantiomer (1).

Dexlansoprazole is the first PPI to utilize Dual Delayed Release (DDR) technology, designed to optimize plasma concentration and prolong acid suppression (2). There are claims that its enhanced bioavailability and reduced plasma clearance contribute to superior efficacy over racemic lansoprazole in healing erosive esophagitis (EE) and managing gastroesophageal reflux disease (GERD) symptoms (3,4). However, dexlansoprazole is more than four times the cost of lansoprazole in British Columbia, raising concerns regarding cost-effectiveness. We aim to evaluate whether dexlansoprazole is truly superior to its parent and to compare the efficacy and safety of the single enantiomer with the racemic formulation.

Esomeprazole / Omeprazole

Omeprazole is a proton pump inhibitor (PPI) consisting of a 1:1 racemic mixture of the R-(+)- and S-(-)-enantiomers (5). Esomeprazole, in contrast, is the pure S-(-)-enantiomer and was the first PPI developed as a single enantiomer derived from its racemic parent compound (6).

Esomeprazole exhibits pharmacokinetic differences, including reduced first-pass metabolism and lower plasma clearance, resulting in increased bioavailability and higher peak plasma concentrations compared with racemic omeprazole (5,7). However,

whether these pharmacokinetic advantages translate into clinically meaningful benefits remains uncertain.

Esomeprazole has been promoted as superior to omeprazole for healing erosive esophagitis (EE) and managing gastroesophageal reflux disease (GERD) symptoms (8). Its cost—more than double that of omeprazole—raises questions regarding cost-effectiveness. Prior studies frequently compared esomeprazole 40 mg with omeprazole 20 mg, which are not equipotent doses. This review focuses on equipotent dosing (20 mg vs. 20 mg) to determine whether esomeprazole offers genuine clinical advantages.

Overall

This review aims to critically evaluate whether single-enantiomer formulations—escitalopram, esomeprazole, and dexlansoprazole—offer clinically meaningful benefits over their racemic predecessors, considering efficacy, safety, and cost. By focusing on equipotent dosing and patient-centered outcomes, this work seeks to inform evidence-based prescribing and support rational use of these medications in clinical practice.

Methods

We assessed utilization and comparative efficacy of selected racemic drugs and their marketed enantiomers in British Columbia (BC), Canada. Prescription data were obtained from the PharmaNet database, which captures all prescriptions filled in BC pharmacies. For antidepressants, we examined the annual prevalence of use (per 1000 persons) for the top nine most prescribed agents from 2000–2022, including adults aged ≥ 19 years with depression identified through hospital admissions, emergency department visits, or family physician billings. For proton pump inhibitors (PPIs), we assessed the top 200 most prescribed drugs from January 1 to May 31, 2024, focusing on omeprazole/esomeprazole and lansoprazole/dexlansoprazole.

Eligible studies for comparative efficacy were head-to-head randomized controlled trials (RCTs) in adults receiving equipotent doses for major depressive disorder (MDD) for the escitalopram-citalopram pair, or acid-related disorders, including erosive esophagitis (EE) and gastroesophageal reflux disease (GERD) for the dexlansoprazole-lansoprazole and esomeprazole-omeprazole pairs. Outcomes of interest included clinical response and remission for MDD, EE healing, symptom relief, and adverse drug reactions (ADRs). Surrogate endpoints, such as intragastric pH control, were excluded due to limited patient-centered relevance (9,10).

A systematic literature search was conducted in MEDLINE, Embase, PubMed, Cochrane CENTRAL, and Epistemonikos from inception to June 30, 2024. Canadian

product monographs and regulatory documents from Health Canada and the US FDA were reviewed to supplement published data. For antidepressants, recent systematic reviews were used to identify head-to-head RCTs comparing escitalopram and citalopram. For PPIs, FDA assessment files and published equipotency data (e.g., esomeprazole 20 mg \approx omeprazole 32 mg) were consulted to ensure appropriate dose comparisons (11,12).

Study outcomes were evaluated for clinical significance and internal validity. Risk of bias was assessed using the Cochrane RoB-2 tool, examining domains such as randomization, missing outcome data, and selective reporting (13,14). For dichotomous outcomes, the fragility index (FI) was calculated to determine the robustness of statistically significant results. An FI of zero indicates extreme fragility, whereas higher values reflect more robust findings. FI was interpreted alongside the number of participants lost to follow-up or otherwise excluded to assess confidence in reported significance (15).

Results

Escitalopram vs. Citalopram

Since 2009, escitalopram has become the predominant antidepressant in BC from 2013–2022 (32 per 1000 persons in 2022), while citalopram use declined (12 per 1000 persons in 2022), despite being the most prescribed antidepressant from 2001–2011.

Study Selection and Characteristics

We identified 12 RCTs (N=2,552) comparing escitalopram and citalopram in adults with MDD (16). All studies were at high risk of bias (14).

Clinical Efficacy

Efficacy differences did not cross minimal clinically important difference thresholds in any RCT. Three trials reported significant differences favoring escitalopram for response or remission, but two of these findings were fragile (16).

Four RCTs reported “early symptom improvement” by Week 1; however, no sustained advantage was demonstrated at later timepoints. Week 1 differences did not exceed minimal clinically important differences in two trials and were indeterminable in the remaining two (16,17).

Adverse Drug Reactions

ADRs were similar between escitalopram and citalopram, with no evidence of differential effects from the R (-) enantiomer or differences in QT prolongation (16).

Dexlansoprazole vs. Lansoprazole

Since 2022, dexlansoprazole has replaced its racemic parent drug, lansoprazole, as the preferred agent for gastrointestinal disorders in BC. In 2024, dexlansoprazole prescriptions surpassed 105,000 (29,099 patients), exceeding the 96,465 prescriptions (19,930 patients) for lansoprazole (18).

Study Selection and Characteristics

We identified 4 head-to-head RCTs (N=4,584) comparing dexlansoprazole and lansoprazole in adult patients with EE and GERD. Attempts to identify equipotent doses were unsuccessful; therefore, all comparative trials were included. Data for dexlansoprazole 90 mg were excluded as this exceeds the recommended daily maximum per the Canadian monograph (19). All studies were at high risk of bias in multiple RoB2 domains (2,20,21).

Clinical Efficacy

The Sharma Studies 1 and 2 (N=4,092) demonstrated non-inferiority of dexlansoprazole 60 mg compared to lansoprazole 30 mg for healing EE over 8 weeks (2). Superiority was observed only in the crude-rate analysis of Study 1 (FI=4), indicating a fragile finding. No significant difference was observed in severe EE (LA grades C or D).

Lin et al. (N=232) reported dexlansoprazole was more effective for atypical GERD symptoms (cough, globus; FI=19), but not hoarseness (20). For typical GERD symptoms, superiority was seen for heartburn but not acid regurgitation (FI=0, fragile).

Bhatia et al. (N=260) found no statistically significant difference in between dexlansoprazole 60 mg and lansoprazole 30 mg for their primary endpoint, mean changes in Gastroesophageal Reflux Disease Symptom Assessment Scales from baseline to week 8, nor for safety outcomes; FI could not be calculated due to non-dichotomous outcomes (21).

Adverse Events

Across studies, adverse events were comparable, most commonly diarrhea, nausea, vomiting, and headache.

Esomeprazole vs. Omeprazole

Since 2007, esomeprazole use in BC has surpassed omeprazole. By 2024, over 373,000 esomeprazole prescriptions were dispensed to more than 96,000 patients—over four times the 89,000 prescriptions for omeprazole (just over 21,000 patients).

Study Selection and Characteristics

We identified 16 head-to-head RCTs, seven using equipotent doses (N=5,576) (8,22-26). All were at high risk of bias, typically fulfilling four of five RoB-2 domains. FI was calculable in two studies (22,23); one additional trial could not be assessed due to incomplete withdrawal and follow-up reporting (24).

Pharmacodynamic and Dose Considerations

Four pharmacodynamic studies assessed intragastric pH control, whereas only two studies utilized equipotent doses (N=168) where they found similar ADR incidence (8,27)[me1.1].

Equipotency

Although esomeprazole 20 mg is considered equivalent to omeprazole 32 mg (11), most trials compared 20 mg to 20 mg, creating a non-equipotent comparison that may favor esomeprazole. Regulatory documents caution against superiority claims based on such comparisons (12)

Clinical Efficacy

Twelve trials evaluated EE healing or GERD symptom control (7,22-25,28-32). Among four equipotent RCTs (N=5,408) (22-25), one reported esomeprazole superiority; however, EE healing and heartburn-free nights both had FI=0, indicating fragile findings (22).

Another study reported significant regurgitation relief utilizing esomeprazole compared to omeprazole at weeks 2 and 4 (FI=5 and 6), though fragility conclusions were limited by incomplete reporting such as the absence of withdrawals and loss to follow-up (23). One abstract suggested omeprazole was more effective in severe EE (grades C or D), and another trial found no difference in EE healing (24).

Adverse Events

ADRs were similar across studies and included headaches, abdominal pain, diarrhea, and nausea.

Discussion

Escitalopram and Citalopram

Escitalopram is the most prescribed antidepressant in British Columbia, with its increased use coinciding with a decline in citalopram prescribing. However, the available evidence does not provide convincing support for replacing citalopram with escitalopram in routine clinical practice.

Claims of escitalopram's superiority are partly derived from *in vitro* and *in vivo* behavioral experiments. Preclinical studies suggest that escitalopram may be more efficacious because R-citalopram displaces S-citalopram at the serotonin transporter, and that escitalopram may have a faster onset of action. (33) However, these theoretical pharmacologic differences are not reflected in head-to-head efficacy trials in humans with depression.

With respect to safety, both escitalopram and citalopram are associated with QT prolongation. Although regulatory reports suggest potential differences in the magnitude of this risk, the clinical relevance of such differences remains unclear, as frequently studies either did not observe QT prolongation in either group or did not report on this outcome entirely. (34)

A limitation of this review is that it did not compare escitalopram with other antidepressants. Whether clinically meaningful differences exist between escitalopram and other agents, including SSRIs, SNRIs, mirtazapine, or bupropion, remains uncertain. Overall, the available comparative evidence does not justify the preferential substitution of citalopram with escitalopram based on efficacy or safety.

Dexlansoprazole and Lansoprazole

Dexlansoprazole is among the most prescribed proton pump inhibitors (PPIs) in British Columbia, with increasing use now exceeding lansoprazole prescribing. However, analysis of the available head-to-head randomized controlled trials (RCTs) does not support routine replacement of lansoprazole with dexlansoprazole.

Claims of superiority for dexlansoprazole are largely grounded in pharmacokinetic and pharmacodynamic studies suggesting theoretical advantages of the single enantiomer. However, these studies do not assess clinical outcomes, limiting their relevance to patient care. (4) Across four RCTs evaluating acid-related disorders, no consistent pattern of superior efficacy emerged. Healing rates were high, and 95% confidence intervals overlapped or nearly overlapped, indicating comparable efficacy. (2,35)

Additionally, regulatory reviews concluded that although some statistically significant differences were observed, they were not clinically meaningful and were inconsistent across studies. (35)

Fragility index (FI) analyses further underscored the instability of reported findings. In some trials, such as the Sharma Study 1, losses to follow-up exceeded the FI (LTFU = 46 withdrawals in the lansoprazole group, compared to FI = 4), raising concerns about the validity of statistically significant outcomes. (2) This phenomenon was also seen in the study by Lin et al. for control of GERD symptoms (LTFU = 5, FI = 0). (20) In others, subgroup analyses suggested potential symptom benefits that were not replicated across studies. Overall, results were statistically fragile, and trials were assessed as high risk of bias using the RoB2 tool.

Intragastric pH control was excluded from efficacy assessment because improvements in pH do not reliably correlate with symptom relief or mucosal healing. Indeed, greater pH suppression did not translate into clinically meaningful differences in healing rates, as evidenced by the Sharma studies. (2,9,10,35)

An important methodological limitation across trials was the absence of established equipotent dosing between dexlansoprazole and lansoprazole. Dexlansoprazole 60 mg was frequently compared with lansoprazole 30 mg despite unclear equivalence. Non-equipotent comparisons may exaggerate apparent differences.

Safety outcomes were comparable across treatments, with no meaningful differences in adverse events.

The risk of bias assessment using the Cochrane RoB2 tool revealed that all included studies had a high risk of bias in multiple domains. The studies were all high risk of bias in three out of five domains of bias, while the Lin et al. study was high risk of bias in four out of five domains. (20,36,37) Frequent concerns included unclear allocation concealment, incomplete outcome data, and selective reporting, which can lead to exaggerations in results. The Takeda-sponsored Sharma studies on dexlansoprazole show selective and incomplete reporting, reflecting the well-documented tendency of industry funding to exaggerate treatment effects.

Collectively, the available evidence demonstrates high risk of bias, fragile statistical significance, and inconsistent results. These findings suggest that reported advantages of dexlansoprazole may be overstated. Given the substantially higher cost of dexlansoprazole relative to lansoprazole in British Columbia, and the absence of demonstrated clinical superiority, its preferential use is not supported by the available evidence.

Esomeprazole and Omeprazole

Esomeprazole prescribing in British Columbia has increased dramatically while use of its parent racemic mixture omeprazole use has waned. Despite theoretical pharmacokinetic advantages of the single enantiomer, head-to-head trials using equipotent doses do not demonstrate clinically meaningful superiority of esomeprazole.

Pharmacodynamic studies have shown modest improvements in intragastric pH control with esomeprazole; however, these differences have not translated into improved patient-centered outcomes. Prior research has also highlighted the poor correlation between intragastric pH changes and clinical benefits. (10,38) Trials employing non-equipotent dosing frequently favored esomeprazole, likely reflecting dose-related bias rather than inherent pharmacologic advantage. (8,22,23,28) Hence, regulatory bodies such as the U.S. FDA have advised against claims that esomeprazole offers significant first-line advantages over omeprazole. (27)

In erosive esophagitis, three equipotent RCTs demonstrated inconsistent findings. One trial reported superiority of esomeprazole for healing and heartburn-free nights, but the FI of 0 indicates extreme fragility. (23) Another reported superiority for regurgitation relief but lacked sufficient reporting of baseline symptom prevalence and losses to follow-up to interpret statistical robustness; calculated FI values suggested fragility. (24) A third abstract-only report suggested that omeprazole might be more effective in severe erosive esophagitis. (25) All studies concluded that esomeprazole does not confer additional safety benefits compared with omeprazole.

Equipotency considerations were central to this review. Current evidence indicates that esomeprazole 20 mg corresponds approximately to an omeprazole equivalent dose of 32 mg. (11) Due to formulation constraints, comparisons were often limited to omeprazole 20 mg versus esomeprazole 20 mg, a comparison that inherently favors esomeprazole because of relative dosing differences. Apparent superiority observed in non-equipotent comparisons was not reproduced under equipotent conditions.

Risk of bias assessments determined that all included trials were at high risk of bias. (13,37) Given these methodological weaknesses, such as concerns regarding blinding, incomplete outcome reporting, and potential industry influence, data from these studies was analyzed narratively rather than meta-analyzed to avoid compounding systematic error. Fragility index analyses further demonstrated the instability of statistically significant findings.

From a policy perspective, 2024 data from the BC Ministry of Health show that esomeprazole was prescribed nearly four times more frequently than omeprazole, with

a tenfold difference in total drug cost. Given equivalent efficacy and safety, preferential use of omeprazole could result in substantial cost savings. These conclusions reinforce that prescribing decisions between esomeprazole and omeprazole should be guided by cost-effectiveness rather than perceived pharmacologic superiority.

Overall

Across all three drug pairs, increased uptake of single-enantiomer formulations coincided with declining use of their racemic counterparts. However, head-to-head clinical evidence consistently demonstrates comparable efficacy and safety, with statistically fragile and methodologically limited trials failing to establish meaningful clinical advantages for the single-enantiomer drugs. These findings support cautious interpretation of claimed benefits and emphasize the importance of prioritizing robust clinical evidence and cost-effectiveness in prescribing decisions.

Limitations of our work include the decision to focus on head-to-head RCTs, rather than meta-analyses. However, as stated, pooling trials at high risk of bias risks the production of biased summary estimates. If future low-risk studies become available, meta-analysis may provide additional context.

Conclusion

In conclusion, evidence from head-to-head RCTs demonstrates no consistent evidence for the efficacy or safety advantages of the single-enantiomer drug compared to their parent racemic mixtures. This is seen in trials comparing dexlansoprazole to lansoprazole for acid-related disorders, comparisons of escitalopram to citalopram for MDD, and for studies examining esomeprazole versus omeprazole examining patient-centered outcomes in acid-related disorders. The preferential prescribing patterns for the use of single enantiomers in comparison to their racemic mixtures in BC are not supported by robust evidence.

Data Availability Statement

The British Columbia (BC) Ministry of Health approved access to and use of BC data from the Healthideas data warehouse (Information Sharing Agreement 16-036). Access to data provided by Data Stewards is subject to approval but can be requested for research projects through Data Stewards. The following data sets were used in this study: *PharmaNet*, *Medical Services Plan*, *Discharge Abstract Database*, *National Ambulatory Care Reporting System*, *Client Roster*. Health records for federally insured residents and those receiving benefits through the First Nations Health Benefit Plan were not included in this data access. All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of Data Stewards.

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Declaration of Conflicts of Interest

None.

Human Ethics and Consent to Participate Declarations

None.

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APPENDIX 1: DEXLANSOPRAZOLE AND LANSOPRAZOLE TRIAL SUMMARIES

Author Year (N)	Drug Pairs	Design	Efficacy Outcomes	Safety Outcomes	Risk of Bias	Fragility Index
Sharma et al. 2009 – Study 1 (n=2,038)	LAN30 vs DEX60	RCT	Healing of EE at 8 weeks: LT LAN 86.1% vs DEX 92.3% (NSS); CR LAN 79.0% vs DEX 85.3% (P<0.05). Healing at 4 weeks: LT and CR both >64% (NSS). LA Grade C/D healing at 8 weeks: LT LAN 74.5% vs DEX 88.9% (P<0.05); CR LAN 65.0% vs DEX 79.7% (P<0.05).	Combined ADRs (Studies 1+2): LAN 27.8% vs DEX 30.4% (NSS). Similar ADR profiles; diarrhea most common cause of discontinuation (DEX 0.5%, LAN 0.2%). Four nonfatal PPI-related ADRs (two per group).	High risk: unclear sequence generation, allocation concealment, blinding, selective reporting; industry funded; incomplete outcome data.	Healing of EE (CR): LAN 518/690 vs DEX 545/680; FI = 4 (fragile). Withdrawals: LAN 46; DEX 51.
Sharma et al. 2009 – Study 2 (n=2,054)	LAN30 vs DEX60	RCT	Healing of EE: LT LAN 91.5% vs DEX 93.1% (NSS); CR LAN 84.6% vs DEX 86.9% (NSS). Healing at 4 weeks: LT and CR both >64% (NSS). LA Grade C/D healing at 8 weeks: LT LAN 87.7% vs DEX 87.6% (NSS); CR LAN 78.9% vs DEX 77.8% (NSS).	Combined ADRs (Studies 1+2): LAN 27.8% vs DEX 30.4% (NSS). Similar ADR profile; four nonfatal PPI-related ADRs total.	High risk: same methodological limitations as Study 1.	No statistically significant dichotomous outcomes.
Bhatia et al. 2014 (n=260)	LAN15/30 vs DEX30/60	RCT	Mean GSAS score change: LAN -4.9 vs DEX -4.4 (NSS).	Incidence of ADRs similar between treatment groups.	Unclear risk: abstract-only publication; industry funded.	No statistically significant dichotomous outcomes.
Lin et al. 2020 (n=232)	LAN30 vs DEX60	RCT	Typical GERD symptoms: LAN 81.3% vs DEX 93.0% (P=0.014). Atypical GERD symptoms: LAN 37.9% vs DEX 67.2% (P<0.001).	ADRs not reported.	High risk: unblinded, unclear allocation concealment and selective reporting, incomplete outcome data, non-representative sample.	Typical symptoms: DEX 93/116 vs LAN 87/116; FI = 0 (fragile). Atypical symptoms: DEX 78/116 vs LAN 44/116; FI = 19 (not fragile). Withdrawals: 5 per group.

Abbreviations: LAN = lansoprazole; DEX = dexlansoprazole; RCT = randomized clinical trial; EE = erosive esophagitis; GERD = gastroesophageal reflux disease; NSS = not statistically significant; LT = life-table analysis; CR = crude rate analysis; ADR = adverse drug reaction; GSAS = GERD Symptom Assessment Scale; FI = Fragility Index.

APPENDIX 2: ESOMPERAZOLE VS OMPERAZOLE TRIAL SUMMARIES

Study	Risk of Bias	Efficacy Outcomes	Safety outcomes	Fragility index*
Pharmacodynamic studies				
Lind 2000 N= 38 Crossover ESO40 ESO20 OME20 Duration: Three 5-day periods	High risk Unclear sequence generation, concealment and blinding, unclear selective reporting risk, industry funded	N/A, No reported clinical outcomes	The rate of ADRs were comparable between treatment groups. No serious drug-related ADRs were reported	N/A, No SS significant dichotomous outcomes
Rohss 2002 N= 130 Crossover ESO40 OME40 Duration: Two 5-day periods	High risk Unclear sequence generation and concealment, Unblinded, unclear selective reporting risk, industry funded	N/A, No reported clinical outcomes	The rate of ADRs were comparable between treatment groups. No serious drug-related ADRs were reported	N/A, No SS significant dichotomous outcomes
EE healing				
Kahrilas 2000 ESO40 (n=654) ESO20 (n=656) OME20 (n=650) Duration: 8 weeks	High risk Unclear concealment and blinding, unclear selective reporting risk and incomplete outcome data, industry funded	<u>Proportion of pts with healed EE at week 8</u> ESO20 > OME20 <u>Proportion of pts with healed EE at week 4</u> ESO20 = OME20 <u>HB resolution at week 4</u> ESO20 = OME20 <u>Time to first resolution by day 7</u> ESO20 = OME20 <u>Time to SR of HB by day 28</u> ESO20 = OME20 <u>Percentage of HB-free days (24hr period)</u> ESO20 = OME20 <u>Percentage of HB-free nights</u> ESO20 > OME20	<u>Percentage of ADRs occurred in ≥3% of pts GI system†</u> ESO20 3.7 vs OME20 3.5 Headache ESO20 8.7 vs OME20 6.9 The rate of ADRs were comparable between treatment groups. No serious drug-related ADRs were reported	<u>Proportion of pts with healed EE at week 8</u> ESO20 (590/656) OME20 (565/650) FI: 0 <u>Percentage of HB-free nights</u> ESO20 (518/656) OME20 (501/650) FI: 0 51 withdrew from OME group
Lightdale 2006 OME20 (n=588) ESO20 (n=588) Duration: 8 weeks	Moderate-High risk Unclear blinding, unclear selective reporting risk, incomplete outcome data, industry funded	<u>Proportion of pts with healed EE at week 8</u> ESO20 = OME20 <u>Proportion of pts with healed EE at week 4</u> ESO20 = OME20 <u>HB resolution at week 4</u> ESO20 = OME20 <u>Percentage of HB-free days (24hr period) at week 4</u> ESO20 = OME20 <u>Percentage of HB-free nights at week 4</u> ESO20 = OME20 <u>Cumulative healing rate (all severity grades) at week 8</u> ESO20 = OME20	<u>Percentage of ADRs</u> ESO20 44 vs OME20 43 The rate of ADRs were comparable between treatment groups. No serious drug-related ADRs were reported	N/A, No SS significant dichotomous outcomes
Sierra 2005 N= 320 OME40 ESO40 Duration: 8 weeks	N/A Abstract	<u>Proportion of pts with healed EE at week 8</u> OME40 > ESO40	Not reported	N/A (Abstract)

GERD symptoms				
Armstrong 2004 Study A ESO40 (n=425) ESO20 (n=423) OME20 (n=434) Duration: 4 weeks	High risk Unclear sequence generation, concealment and blinding, unclear selective reporting risk, incomplete outcome data, industry funded	<u>Resolution of HB † at 4 weeks:</u> ESO20 = OME20 <u>Resolution of HB at 2 weeks</u> ESO20 = OME20 <u>Regurgitation relief at 2 and 4 weeks</u> ESO20 > OME20 <u>Dysphagia relief at 2 weeks</u> ESO20 = OME20 <u>Dysphagia relief at 4 weeks</u> ESO20 = OME20 <u>Overall treatment evaluation</u> ESO20 = OME20	The rate of ADRs were comparable between treatment groups. No serious drug-related ADRs were reported	<u>Regurgitation relief at 2 weeks</u> ESO20 (190/285) OME20 (164/288) FI: 5 <u>Regurgitation relief at 4 weeks</u> ESO20 (218/285) OME20 (194/288) FI: 6 Unknown withdrawal number
Armstrong 2004 Study C ESO20 (n=336) OME20 (n=334) Duration: 4 weeks	High risk Unclear sequence generation, concealment and blinding, unclear selective reporting risk, incomplete outcome data, industry funded	<u>Resolution of HB † at 4 weeks</u> ESO20 = OME20 <u>Resolution of HB at 2 weeks</u> ESO20 = OME20 <u>Regurgitation relief at 2 and 4 weeks</u> ESO20 = OME20 <u>Dysphagia relief at 2 and 4 weeks</u> ESO20 = OME20 <u>Overall treatment evaluation</u> ESO20 = OME20	The rate of ADRs were comparable between treatment groups. No serious drug-related ADRs were reported	N/A, No SS significant dichotomous outcomes

ADR = adverse drug reaction; SR= sustained resolution (7 days without heartburn); HB= heartburn; Pts = Patients; ESO40= esomeprazole 40mg; ESO20= esomeprazole 20 mg; OME40= omeprazole 40 mg; SS= statistically significant; EE = erosive esophagitis, FI=fragility index

* Fragility Index: Calculated using <https://clincalc.com/Stats/FragilityIndex.aspx>, determines the number of patients needed to convert from a non-event to an event, to turn a statistical finding into not significant. The larger the fragility index the more robust/better the data are

† Average of the 5 GI symptoms reported (abdominal pain, diarrhea, flatulence, gastritis and nausea)

‡ No Heartburn symptoms within the last 7 days

APPENDIX 3: ESCITALOPRAM AND CITALOPRAM TRIAL SUMMARIES

RCT (first author, year published, total randomized, alternative study ID if applicable)	Risk of Bias	Comparators and Ns	Efficacy	Safety	Fragility index	Funding source
<p>Burke 2002</p> <p>Alternative study IDs: ST-MD-01, 99007</p> <p>N=491</p> <p>Duration: 8 weeks</p>	<p>High</p> <p><i>(Unclear randomization, concealment & blinding, unclear selective reporting risk, industry funded, incomplete outcome data)</i></p>	<p>Placebo</p> <p>ESC 10</p> <p>ESC 20</p> <p>CIT 40</p>	<p>ΔMADRS: ESC20 = CIT40, NSS</p> <p>ΔHAM-D: ESC20 = CIT40, NSS</p> <p>Response: ESC20 = CIT40, NSS</p> <p>CGI-I & CGI-S: ESC20 = CIT40, NSS</p>	<p>% ADR: ESC20 86 vs CIT40 86</p> <p>QT prolongation: Not observed in any group</p> <p>Serious ADR: Not observed in any group</p>	N/A	Forest
<p>Colonna 2005</p> <p>N=357</p> <p>Duration: 24 weeks</p>	<p>High</p> <p><i>(Unclear selective reporting risk, industry funded, incomplete outcome data)</i></p>	<p>ESC 10</p> <p>CIT 20</p>	<p>ΔMADRS: ESC = CIT, NSS</p> <p>Response: Week 8: ESC > CIT, SS</p> <p>Week 24 ESC = CIT, NSS</p> <p>Remission: ESC = CIT, NSS</p> <p>CGI-S: ESC > CIT, SS</p>	<p>% ADR: ESC 63 vs CIT 72</p> <p>QT prolongation: Not observed in any group</p> <p>Serious ADR: Suicide attempt: ESC 3 vs CIT 3</p>	N/A	Lundbeck
<p>Lalit 2004</p> <p>N = 214</p> <p>Duration: 4 weeks</p>	<p>High</p> <p><i>(Unclear randomization & concealment, selective reporting risk, unclear funding, unclear outcome assessment,</i></p>	<p>ESC 10-20</p> <p>CIT 20-40</p> <p>Sertraline 50-100</p>	<p>ΔHAM-D: ESC = CIT, NSS</p> <p>Response: ESC = CIT, NSS</p> <p>Remission: ESC = CIT, NSS</p>	<p>% ADR: ESC 45 vs CIT 58</p> <p>QT prolongation: Not observed in any group</p>	N/A	<p>Torrent</p> <p>(Indian pharma. company)</p>

	<i>incomplete outcome data)</i>		CGI-S & CGI-I: ESC = CIT, NSS	Serious ADR: Not observed in any group		
Lepola 2003 Alternative study ID 99003 N=468 Duration: 8 weeks	High <i>(Unclear randomization, concealment & blinding unclear selective reporting risk, industry funded, incomplete outcome data)</i>	Placebo ESC 10-20 CIT 20-40	Δ MADRS: ESC = CIT, NSS Response: ESC > CIT, SS Remission: ESC > CIT, SS CGI-S & CGI-I: ESC = CIT, NSS	% ADR: ESC 70 vs CIT 65 QT prolongation: Not observed in any group Serious ADR: Not observed in any group	Response: ESC 99/155 vs CIT 84/160 (SS) Response FI: 0 Remission: ESC 81/155 vs CIT 68/160 (SS) Remission FI: 0 8 withdrew from citalopram	Lundbeck
Moore 2005) N=280 Duration: 8 weeks	High <i>(Unclear randomization & concealment, unclear selective reporting risk, industry funded, incomplete outcome data)</i>	ESC 20 CIT 40	Δ MADRS: ESC > CIT, SS Response: ESC > CIT, SS Remission: ESC = CIT, NSS CGI-S: ESC = CIT, NSS	% ADR: ESC 15 vs CIT 16 QT prolongation: Not reported Serious ADR: Suicide: CIT 1	Response: ESC 105/138 vs CIT 87/142 (SS) Response FI: 6 15 withdrew from citalopram	Lundbeck
Ou 2011 N=232 Duration: 6 weeks	High <i>(Unclear selective reporting risk, unclear funding, high incomplete outcome data)</i>	ESC 10-20 CIT 20-40	Δ HAM-D: ESC = CIT, NSS Response: ESC = CIT, NSS Remission: ESC = CIT, NSS	% ADR: ESC 29 vs CIT 30 QT prolongation: Not reported Serious ADR: Not observed in any group	N/A	National institutes of Pharmaceutical Research and Development Co., Ltd., and all drugs were provided by the company
Yevtushenko 2007 N=322 Duration: 6 weeks	High <i>(Unclear randomization & concealment, unclear selective reporting risk, unclear funding, unclear incomplete outcome data)</i>	ESC 10 CIT 10 CIT 20	Δ MADRS: ESC > CIT10/20, SS Response: ESC > CIT10/20, SS Remission: ESC > CIT10/20, SS	% ADR: ESC 6 vs CIT 16 QT prolongation: Not reported Serious ADR: Not observed in any group	Response: ESC 103/108 vs CIT20 90/108 (SS) Response FI: 4 (fragile) Remission: ESC 97/108 vs	OOO ARBACOMM, Moscow, Federation of Russia

			CGI-S & CGI-I: ESC > CIT, SS		CIT20 55/108 (SS) Remission FI: 31 (robust) 1 withdrew escitalopram and 8 from citalopram	
SCT-MD-02 Alternative study ID 99008 N=386 Duration: 8 weeks	High <i>(Unclear randomization, low risk allocation concealment, unclear blinding, high risk due to LOCF/missing outcome data, unclear selective outcome reporting, manufacturer- funded)</i>	ESC 10-20 CIT 20-40 Placebo	Change from baseline in MADRS total at week 8 ESC=CIT, NSS Response: ESC=CIT, NSS Remission: NR CGI: ESC=CIT, NSS	% ADR: ESC 79vs CIT 81 QT prolongation: not observed in any group Serious ADR: ESC 1.6% vs CIT 0.8%	N/A	Forest Laboratories Inc
Hu 2009 N=48 Duration: 6 weeks	Unclear <i>(Unclear randomization, low risk allocation concealment, unclear blinding, high risk due to LOCF/missing outcome data, unclear selective outcome reporting, high risk for funding)</i>	ESC 10-20 CIT 20-40	Δ HAM-D: Week 1: ESC > CIT, SS Week 2-6: ESC = CIT, NSS Response: ESC =CIT, NSS Remission: ESC = CIT, NSS CGI: ESC = CIT, NSS	% ADR: ESC 20 vs CIT 35 QT prolongation: Not reported Serious ADR: Not observed in any group		Medication provided by Shenzhen Sansun Pharmaceutical Co., Ltd
Jiang 2009 N= 64	Unclear <i>(Unclear randomization, low risk allocation concealment, unclear blinding, high risk due to LOCF/missing</i>	ESC 10-20 CIT 20-40	Δ HAM-D Week 1: ESC > CIT, SS Week 2-6: ESC = CIT, NSS	% ADR: ESC 42vs CIT 47 QT prolongation: Not reported		Not reported

Duration: 6 weeks	<i>outcome data, unclear selective outcome reporting, unclear funding)</i>			Serious ADR: Not observed in any group		
Lü 2013 N=42 Duration: 6 weeks	Unclear <i>(Unclear randomization, low risk allocation concealment, unclear blinding, high risk due to LOCF/missing outcome data, unclear selective outcome reporting, unclear funding)</i>	ESC 10-20 CIT 20-40	ΔHAM-D Week 1: ESC = CIT, NSS Week 2-6: ESC = CIT, NSS Response: ESC = CIT, NSS Remission: ESC - CIT, NSS	% ADR: ESC 25 vs CIT 31.8 QT prolongation: Not reported Serious ADR: Not observed in any group		Not reported
Li 2006 N = 56 Duration: 6 weeks	Unclear/High <i>(Low risk for sequence generation and allocation concealment, unclear for blinding, high risk for missing outcome data, unclear for selective outcome reporting, high risk for funding)</i>	ESC 10-20 CIT 20-40	ΔHAM-D: ESC = CIT, NSS Response: ESC = CIT, NSS Remission: ESC = CIT, NSS	% ADR: ESC 33 vs CIT 31 No QT prolongation: Not observed in any group Serious ADR: Not observed in any group	N/A	Chengdu Kelun Pharmaceutical Research Institute
Li 2010 N=48 Duration: 6 weeks	Unclear <i>(Unclear randomization, low risk allocation concealment, unclear blinding, high risk due to LOCF/missing outcome data, unclear selective outcome reporting, unclear funding)</i>	ESC 10-20 CIT 20-40	ΔHAM-D Week 1: ESC > CIT, SS Week 2-6: ESC = CIT, NSS Response: ESC = CIT, NSS Remission: ESC = CIT, NSS	% ADR: Unable to determine QT prolongation: Not observed in any group Serious ADR: Not observed in any group	N/A	Jiangsu Aosaikang Pharmaceutical Co., Ltd.
Li 2014	High <i>(Unclear sequence</i>		Change in HAMD	% ADR: ESC 73 vs CIT 74		National Major Project for IND, Clinical

<p>RCT 1 N=268, RCT 2 N=269, RCT 3 N=240</p> <p>Duration: 8 weeks</p>	<p><i>generation, allocation concealment, missing outcome data, selective outcome reporting; low risk funding bias; no individual RCT details reported)</i></p>		<p>ESC=CIT, NSS all 3 RCTs</p> <p>Response:</p> <p>ESC=CIT, NSS all 3 RCTs</p> <p>Remission:</p> <p>ESC=CIT, NSS all 3 RCTs</p> <p>CGI</p> <p>ESC=CIT, NSS all 3 RCTs</p>	<p>QT prolongation:</p> <p>Not reported</p> <p>Serious ADR:</p> <p>Not observed in any group.</p>		<p>tech-platform for evaluation of new drugs in psychiatry</p> <p>(No. 2012ZX09303- 003) and the Shanghai Health talent professional project (No. XBR2011049).</p>
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