Application for Inclusion to the 21st Expert Committee on the Selection and Use of Essential Medicines:

ESCITALOPRAM

December 7, 2018

Submitted by:
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1. Summary statement of the proposal for inclusion of escitalopram

This is a proposal to include escitalopram on the core WHO Model List of Essential Medications (EML) to treat adults age 18+ with major depressive disorder. The latest EML includes a member of the tricyclic antidepressant (TCA) class, amitriptyline, and one member of the selective serotonin reuptake inhibitor (SSRI) class, fluoxetine. We provide a review of evidence on efficacy, safety, availability, and cost-effectiveness of escitalopram, another member of the SSRI class, for the treatment of depression in adults.

Escitalopram was first introduced to market in 2002 in the United States and has become a generically available product as of 2012. It approved for the treatment of major depression, as well as generalized anxiety disorder, in several countries and is a frequently prescribed medication globally for these indications. Since it has become generic, its cost has dropped significantly, increasing its availability globally as well as its cost-efficacy.

The antidepressant class of SSRIs is recommended as first-line treatment for depression per several international guidelines. Research exploring differences in efficacy and tolerability between the members of the SSRI class has expanded significantly in the last several years. A major, GRADE-reviewed, network meta-analysis of over 500 double-blinded randomized controlled trials published up until 2016, found small but significant advantages to escitalopram over other SSRIs and other antidepressants on both efficacy and tolerability measures. Based on these results, escitalopram is one of the best, if not the best, generically available antidepressant.

Escitalopram may confer a particular advantage over the currently listed antidepressants on the EML because of an improved side-effect profile as compared to amitriptyline and no potent effect on hepatic cytochrome enzymes, in contrast to fluoxetine. These features of escitalopram may be particularly useful in the treatment of the elderly, who may not be able to tolerate the side effects of amitriptyline long enough to stay on the medication and who may be on other medications whose metabolism is altered by fluoxetine. Given that peak prevalence of depression is in older persons above age 55, it is particularly important to include safe, tolerable medications for the treatment of depression to target this population.

Cost-effectiveness analyses, with and without pharmaceutical funding, have largely found escitalopram to be equal or better than comparator drugs. As the majority of these studies were completed while escitalopram was under patent, it is likely that the cost-effectiveness profile of escitalopram has only improved since 2012.

This proposal therefore argues for inclusion of escitalopram as an efficacious, tolerable, and cost-effective medication for the treatment of depression.
2. Relevant WHO technical department and focal point

Dr. Tarun Dua, MD, MPH  
Programme Manager  
Department of Mental Health and Substance Abuse  
WORLD HEALTH ORGANIZATION  
E-mail: duat@who.int  
Phone: 41 22 7913059
3. Name of organization consulting/supporting the application

Stanford University
4. International Nonproprietary Name (INN, generic name) of the medicine

INN: escitalopram
ATC: N06AB10
5. Formulations of escitalopram proposed for inclusion

Core List
- Tablet 10 mg

Current Market Availability:

Antidex (CR, DO, GT, HN, NI, PA, SV); Asitaloks (UA); Celtium (EC); Ciletrenta (LK); Cipralex (AE, AT, BG, BH, CH, CY, CZ, DE, DK, EE, EG, ES, FI, GB, GR, HR, HU, IE, IL, IN, IQ, IR, IS, IT, JO, KW, LB, LT, LY, MT, NO, OM, PK, PL, PT, QA, RO, RU, SA, SE, SI, SK, SY, TR, YE); Citalam (BD); Citalo (KW); Citao (TW); Citaplex (KR); Clementin (TR); Conjupram (PH); Depram (ID); Depesan (UA); Depsit (LK); E-Zentius (PE); Ecnil (LK); Edpa (KR); Elapram (ID); Elxion (ID); Emeram (BD, TW, UY); Esciprex (IE); Escital (KR); Escitalpro (IE); Escivex (PH); Esidep (TH); Esipram (AU); Estialo (AU, HK, PH); Eslopran (CO); Esopam (TH); Esoplex (LB); Esram (HR); Estimex (PY); Esto (IL); Estoram (KR); Etalopre (IE); Feliz S (PH); Feliz S 10 (ZW); Feliz S 20 (ZW); Feliz-20 (TZ); Ifran (CL, CO); Jovia (PH); L-Xapam (KR); Leeo (TW); Lenuksyn (UA); Lepax (TW); Lexacure (KR); Lexam (AU); Lexapram (KR); Lexapro (AR, AU, BB, BM, BR, BS, AZ, CN, EC, CY, HK, IE, JM, JP, KR, MY, NL, NZ, PE, PH, PR, SG, SR, TH, TT, TW, VE); Lexaprox Meltz (KR); Lexatin (KR); Lexitam (KR); Lexin (PH); Lokxalate (AU); Neolexa (LK); Neopra (HK); Newpram (KR); Nexito (PH); Nodep (LK); Oxpak (LK); Pramokline (MY); Recita (IN); S-Celepra (PH); S-Opropram (HK, MT); Sarapram (KR); Seropam (BD); Seroplex (FR); Sipremarka (BE); Spador (BD); Talopram (PY); Zelax (LB, QA); Zytafram (PH)

Lexi-comp

1. **Aciprex (DI)** (Form Not Given) Biofarm, Pol. Poland 8298136 ESCITALOPRAM - DRUGDEX
2. **Aloce (FM)** (Form Not Given) Miklich, Port. Spain 8411708 ESCITALOPRAM - DRUGDEX
3. **Alvoplex (FM)** (Form Not Given) Alvogen, Cz. Czech Republic 8153345 ESCITALOPRAM - DRUGDEX
4. **Anxila** (Form Not Given) KRKA, Cz. Czech Republic 8289110 ESCITALOPRAM - DRUGDEX
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6. **Benel** (Form Not Given) Formalider, Denm. Spain 8325098 ESCITALOPRAM - DRUGDEX
7. **Betesda** (Form Not Given) Axxon, Pol. Poland 8257956 ESCITALOPRAM - DRUGDEX
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9. **Calolex (FM)** (Form Not Given) Chanelle, Port. Ireland 8343924 ESCITALOPRAM - DRUGDEX
10. **Calolex** (Form Not Given) Chanelle, Denm. Ireland 8382392 ESCITALOPRAM - DRUGDEX
11. **Celtium** (Form Not Given) Saval, Chile Chile 8176843 ESCITALOPRAM -
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Source: Micromedex
6. Listing requested as

Individual medicine
7. Treatment details for escitalopram

7.1 Dosing and Duration

**Escitalopram dosage forms (1):**

- Tablet: 5 mg, 10 mg (scored), 20 mg (scored)
- Capsule: 5 mg, 10 mg, 20 mg
- Oral Solution: 5 mg/5 mL

**Usual dosage range (1):**

- 10-20 mg/day

**Onset of action (1):**

2-4 weeks, if not working within 6-8 weeks it may require a dosage increase or it may not work at all.

**Long-term use (1):**

May continue for many years to prevent relapse of symptoms. It is indicated for the acute and maintenance treatment of major depressive disorder in adults and adolescents 12 to 17 years of age.

**Dosage guidelines for oral formulation approved uses for escitalopram (1,2):**

Escitalopram has US Food and Drug Administration (FDA)-approved uses for major depressive disorder in adults (ages 18 and older) and adolescents (between ages 12-17) and generalized anxiety disorder in adults.

Unless otherwise noted escitalopram may be administered on a once daily schedule morning or evening.

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7.2 Special Populations (1,2)

**Elderly:**

10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment. Risk of SIADH with SSRIs is higher in elderly.
**Children and adolescents:**
Approved for depression in adolescents aged 12-17. Use with caution, observing for activation of known, or unknown, bipolar disorder and/or suicidal ideation, and inform parents or guardians of the risk so they can help observe the child or adolescent. Decreased appetite and weight loss have been observed with use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with escitalopram.

**Renal impairment:**
No dose adjustment is necessary for patients with mild or moderate renal impairment. Escitalopram should be used in caution in patients with severe renal impairment.

**Hepatic impairment:**
Recommended dose 10 mg/day

**Pregnancy:**
As controlled studies are few in pregnant women, escitalopram is not generally recommended for use during pregnancy, especially during first trimester. However, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus. Exposure to SSRIs early in pregnancy may be associated with risk of septal heart defects (absolute risk small). Neonates exposed to SSRIs or SNRIs late in third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include: respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying.

**Breast feeding:**
Some drug is found in mother’s breast milk. If child becomes irritable or sedated, breast feeding, or drug, may need to be discontinued.

7.3 **Pharmacokinetics** (1,2)
Metabolized by CYP3A4 and -2C19. Escitalopram is metabolized by multiple enzyme systems, inhibition of single enzyme may not appreciably decrease escitalopram clearance.

No significant action on CYP450 enzymes.

- Mean terminal half-life: 27-32 hours
- Time to steady-state in plasma concentration with once-daily dosing: 1 week
- The tablet and oral solution dosage forms are bioequivalent
- Time to peak blood levels: 5 hours
- Absorption not affected by food

7.4 **Other Considerations**

**Overdose (2):**
Overdose with escitalopram has been rarely reported. Symptoms of overdose, alone or in combination with other drugs and/or alcohol, include convulsions, coma, dizziness, hypotension,
insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose.

In management of overdose establish and maintain an airway to ensure adequate ventilation and oxygenation. Consider gastric evaluation by lavage and activated charcoal. Monitor cardiac and vital signs, along with general supportive care. There are no specific antidotes for Lexapro.

**Dependence or abuse (1):**
None known.

**Discontinuation (1,2):**
Taper not usually necessary, but it may be helpful to taper in order to avoid potential withdrawal reactions. Many people tolerate 50% dose reduction for 3 days then another 50% reduction for 3 days then discontinuation. If adverse reactions including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania raise the dose to stop symptoms and then restart withdrawal much more slowly.

**Storage and handling (2):**

- Store escitalopram at 25°C (77°F); excursions permitted to 15–30°C (59–86°F)
- Keep escitalopram bottle closed tightly

### 7.4 Guideline Recommendations

The WHO guidelines for the treatment of depression does not distinguish between different members of the SSRI class, though recommends that tricyclic antidepressants or fluoxetine should be considered in adults with a moderate to severe depressive episode/disorder (3). These treatments should also be considered in women suffering from a depressive episode who are planning a pregnancy, pregnant or breastfeeding, if drug treatment is required. The WHO guidelines recommend avoiding use of TCAs in the elderly. The strength of these recommendations is rated as “standard.”

Given no specific recommendations on utilization of different members of the SSRI class, guidelines from different countries were consulted and are summarized below.

The National Institute for Health and Care Excellence (NICE) guidelines from the United Kingdom (UK) list several benefits to the class of SSRIs, as it is associated with fewer anticholinergic side effects, less likely to cause postural hypotension or sedation, less necessity for dosage titration which implies that subtherapeutic doses are less likely to be prescribed, less cardiotoxic, and much safer in overdose than the TCAs or MAOIs. The guidelines specify that fluvoxamine, fluoxetine and paroxetine are inhibitors of various hepatic cytochrome metabolizing enzymes which therefore precipitate several significant drug-drug interactions. NICE identifies sertraline as less problematic (though enzyme inhibition is dose-related) in this regard and citalopram and escitalopram as relatively safe. In accordance, the NICE guidelines recommend a generic SSRI as the first choice given its favorable risk-benefit ratio. It specifically
cautions that SSRIs may increase risk of bleeding and to be particularly cautious in the elderly who are concurrently taking an NSAID or aspirin. In terms of recommendations relevant to the current antidepressants listed on WHO’s EML, amitriptyline and fluoxetine, the guidelines urge clinicians to consider that venlafaxine, duloxetine, and TCAs confer an increased likelihood of patient discontinuation due to side effects and that TCAs specifically confer a risk of orthostatic hypotension and arrhythmias (4).

Compared to the 2010 guideline, the 2018 guideline included a new section on escitalopram specifically, as several studies have been published about its efficacy since 2010. The NICE guidelines summarize escitalopram as superior to placebo in the treatment of depression, with some evidence suggestive of more efficacy at 20 mg compared to 10 mg, but at the cost of more side effects. It designated escitalopram as more effective than citalopram (small effect size) and at least as effective as other SSRIs, if not perhaps more effective (statistically significant differences, but of small effect size of unlikely clinical importance), with marginally better tolerability, except as compared to sertraline. Overall, the NICE guidelines concluded that choice of antidepressant should largely be guided by side-effect profile, patient preference, and previous treatment experience (4).

The Canadian Network for Mood and Anxiety Treatments (CANMAT) guideline for the treatment of depression, published in 2016, names escitalopram as a “first line” treatment, along with all other SSRIs, including fluoxetine. Amitriptyline is listed as “second line” treatment. The guidelines specifically summarize the results of its literature search as “some antidepressants have modest superiority for treatment response, particularly escitalopram, mirtazapine, sertraline, and venlafaxine.” Escitalopram is listed as a drug that confers “minimal or low potential” for drug-drug interactions, in contrast to fluoxetine which confers a “higher potential,” given that it is a potent CYP2D6 and CYP2C19 inhibitor (5).

The American Psychiatric Association (APA) guidelines, published in 2010, did not find any evidence to suggest superiority of another antidepressant class or agent over the SSRIs, and named one meta-analysis suggestive of slight superiority of escitalopram over other SSRIs and venlafaxine and another suggestive of escitalopram, sertraline, venlafaxine, and mirtazapine as superior to duloxetine, fluoxetine, fluvoxamine, and paroxetine. These guidelines do not reflect the greater body of evidence comparing different antidepressants that have been published since 2010. The guidelines recommend starting at 10 mg/day with a maximum dose of 20 mg/day. The APA guidelines also support escitalopram’s favorable drug-drug interaction profile over that of fluoxetine, fluvoxamine, and paroxetine (6).

Royal Australian and New Zealand College of Psychiatrists (RANZP) recommends SSRIs, including escitalopram, as first-line treatment due to its reasonable efficacy and tolerability profile. TCAs are designated as second-line treatment due to tolerability and safety concerns (7). The South African Society of Psychiatrists guidelines also recommend SSRIs, including escitalopram, or SNRIs as first-line treatment (8).

The American Geriatrics Society has developed a list of medications to avoid in the elderly due to various side effects, known as the Beers’ Criteria (9). Amitriptyline as well as several other
members of the tricyclic antidepressant class (clomipramine, desipramine, imipramine, nortriptyline, for example) and one SSRI (paroxetine), are strongly recommended with high quality evidence to avoid use in the elderly due to its “highly anticholinergic, sedating, and cause orthostatic hypotension” properties. SSRIs (along with TCAs, SNRIs, and mirtazapine) are strongly recommended with moderate evidence to “use with caution” in the elderly due as these medications may cause or exacerbate syndrome of inappropriate anti-diuretic hormone secretion. The Beers Criteria also strongly recommends, with high quality evidence, to “avoid” SSRIs in patients with a history of fractures or falls as they may cause or exacerbate ataxia, impaired psychomotor function, syncope, or additional falls. SSRIs and TCAs should be avoided (strong recommendation, moderate quality evidence) if the patient is already on ≥2 CNS-active drugs to minimize increased risk of falling (9). A similar Italian guideline lists amitriptyline as a drug that should be “always avoided,” due to its side effect profile as mentioned above, and fluoxetine as “rarely appropriate” for the elderly ≥ 65 years old, citing its long half-life and presence of active metabolites as problematic (10). The guideline recommends consideration of fluoxetine when other agents have failed.

In summary, several international guidelines recommend SSRIs as a first-line treatment for depression (4–8) and some guidelines note possible superiority of escitalopram over other SSRIs with respect to efficacy and tolerability (4–6). With respect to the elderly, SSRIs are considered first-line pharmacotherapy, with strong recommendations against use of TCAs (9,10). Fluoxetine, the other antidepressant on the WHO EML, confers limitations due to its CYP enzyme inhibition (4–6,9,10), that may limit its use in patients on multiple other medications, such as the elderly.
8. Information supporting the public health relevance

8.1 Disease Burden
Depression is estimated to affect 322 million people as of 2015, approximately 4.4% of the global population. It has a peak prevalence both in men (5.5%) and women (7.5%) in later adulthood (ages 55-74). Depression was responsible for over 50 million years lived with disability (YLDs) globally in 2015 and, at 7.5% of all YLDs, is the largest single contributor to non-fatal health loss (11). Over 80% of this burden is shouldered by low- and middle-income countries. To use a related metric, another study using data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 estimated that depression accounted for approximately 74.4 million disability-adjusted life years (DALYs) worldwide, representing 40.5% of DALYs caused by mental and substance use disorders and 3.0% of all DALYs worldwide (12).

The class of antidepressants known as the selective serotonin reuptake inhibitors (SSRIs) are broadly recommended as the first-line treatment for depression (4–8). Escitalopram is the latest drug to be added to the class of SSRIs and recently lost patent in 2012. Whereas citalopram is a racemic mixture of the active ingredient, escitalopram contains only the s-enantiomer of citalopram, 100 times more potent and with theoretically fewer side effects than r-citalopram (4).

Given that approximately 20-30% of patients do not respond adequately to their first antidepressant (assuming appropriate dosage, treatment time, and medication adherence) and that about 50% of this population respond to their second (4), there should be a safe, efficacious, antidepressant available as an alternative. The U.S. guidelines draw no distinction between switching to an agent of the same class or to an agent of a different class (6), nor does the U.K. guidelines, though the latter suggests a small efficacy advantage to switching to venlafaxine or escitalopram of dubious clinical significance (4). Given numerous considerations in the prescription of amitriptyline that may limit its clinical use, escitalopram, for its efficacy, tolerability, minimal potential for drug-drug interactions, is not only useful as a first-line treatment in several populations, but also as a switch option for those who do not demonstrate sufficient improvement on fluoxetine.

8.2 Assessment of Current Use
Escitalopram was the fourth most frequently prescribed antidepressant in the United States at 25.2 million prescriptions in 2016, and the 26th most prescribed drug overall. Comparatively, trazodone ranked #24 overall with 25.3 million prescriptions, citalopram #21 overall with 26.4 million prescriptions, and sertraline #14 overall with 37.1 million prescriptions. The indication for these medications, however, was not specified, and could encompass treatment for insomnia (particularly likely for trazodone) (13). The Centers for Disease Control and Prevention (CDC) in the United States analyzed Truven Health’s 2008–2013 MarketScan Commercial Claims and Encounters databases, a large convenience sample of clients with private employer-sponsored insurance, to assess outpatient prescription antidepressant claims for women aged 15-44 years (reproductively aged), approximately 5.8 million women per year. From 2008-2013, the most common antidepressant prescriptions were sertraline (an average of 3.3% over this time period), bupropion (2.7%), citalopram (2.6%), escitalopram (2.5%), and fluoxetine (2.3%) (14).
A study of Australia’s Drug Utilisation Sub-Committee, which contains outpatient prescription data of both subsidized and non-subsidized drugs including prescriptions from private clinics, reported antidepressant use over a 12-year period (2000-2011) as defined daily dose (DDD) per 1000 persons of the population per day (15). Sertraline was the highest dispensed in 2011 at 21.4% of total DDDs/1000/day, followed by escitalopram at 14.7% and venlafaxine at 13.9%. Fluoxetine represented 7.1%.

In a study of 706 patients aged 16-65 who met criteria for depression, recruited from 16 centers across India (with diversity in facility-type, from teaching institutions to privately run psychiatric clinics), escitalopram was the most commonly prescribed antidepressant at 40% of all antidepressant prescriptions, followed by sertraline at 17% and fluoxetine at 16% (16). A larger cross-sectional study published by the same group in 2014, consisting of 4480 patients aged 16-65 using psychiatric services across 11 centers, found similar results: 33.8% of the sample received prescriptions for escitalopram, making it the most frequently prescribed antidepressant as compared to sertraline 19%, amitriptyline 11.5%, and fluoxetine 9.3% (17). An analysis of the Hospital Purchase of Drug Information System from 32 hospitals in different administrative districts of China’s Wuhan province, representing both urban and rural hospitals, found that as of 2012, escitalopram had the second highest utilization (0.589) to paroxetine (0.639), measured as defined daily doses per 1000 inhabitants per day (18). In 2013, across 40 psychiatric centers in 10 Asian countries (China, Japan, Korea, Singapore, Taiwan, India, Indonesia, Malaysia, and Thailand) included in the Research on Asia Psychotropic Prescription (REAP) project, who were prescribed an antidepressant in a three-month window in 2013 (19). Fluoxetine (16%), sertraline (15%), and escitalopram (14%) were the top 3 prescribed antidepressants.

In a prospective, descriptive cohort study of “nationally representative medicine claims data submitted to a privately owned South African pharmaceutical benefit management (PBM) company,” representing all antidepressant prescriptions for 407,586 patients over a 6-year study period from 2006-2011, escitalopram was the second most prescribed antidepressant at 14.6% of all antidepressant prescriptions, with venlafaxine at 14.9% topping the list. By contrast, fluoxetine and amitriptyline made up 6.0% of the prescriptions each (20).

A study of France’s main national health insurance (representing 75% of the French population), SNIIRAM (Système National d'Information Inter- Régimes de l'Assurance Maladie) database records, specifically isolating new antidepressant prescriptions (the client must not have had any psychiatric diagnoses in the past 4-5 years and no prior prescription of psychotropics in 2009 and 2010) in 2011, found that of the 998,710 adults initiating an antidepressant, escitalopram was prescribed the most frequently (33%), followed by paroxetine (15%), amitriptyline (11%), fluoxetine (7%) and venlafaxine (7%) (21). In a Danish study evaluating prescribing patterns in 2009-2010, escitalopram was more commonly chosen as the first SSRI over citalopram and sertraline (n = 65,313 prescriptions for treatment-naïve patients, 19% of which were for escitalopram with higher rates when psychiatrists and hospital physicians were the prescribers) (22).

8.3 Target Population
Escitalopram has been most studied in adult populations, ages 18 and up. The efficacy of escitalopram in the adult population is detailed below, but escitalopram offers a distinct
advantage over the currently listed WHO EML antidepressants, amitriptyline and fluoxetine, particularly for the elderly. Escitalopram is metabolized by three CYP450 isozymes in parallel and is neither an inducer nor a significant inhibitor of CYP450. Moreover, since its protein-binding is low, escitalopram presents a low risk of clinically relevant drug–drug interactions (23). Several national guidelines cite escitalopram’s pharmacological profile as advantageous over fluoxetine (see section 7 for more details) and its adverse event profile as advantageous over TCAs, like amitriptyline, which are recommended by a number of national treatment guidelines as second-line treatment for the treatment of depression (4–6).

8.4 Likely Impact of Treatment on the Disease
Antidepressants take several weeks to take effect (4–7) but a patient's tolerance of the medication may not be sufficient. There is evidence to suggest improved tolerability over currently listed WHO EML antidepressants (24), thereby increasing the likelihood that patients stay on the medication long enough and that escitalopram may be safer in populations for whom fluoxetine or amitriptyline is not an ideal choice – for example, in patients on drugs whose metabolism may be affected by fluoxetine (4–6), or patients with heart conditions such as cardiac instability or ischemia for whom the risk of arrhythmia with amitriptyline is too great (4,6), or elderly patients for whom amitriptyline is strongly recommended to avoid to prevent morbidity related to its side effects (9,10). Given the estimate that the peak prevalence in both men and women is in older adulthood (ages 55-74), there is likely a worldwide population that remains un- or undertreated, a group in which fluoxetine and amitriptyline may be relatively contraindicated, calling for a need to include a more tolerable and efficacious medicine, one that the population may adhere to drug treatment long enough to appreciate benefit.
9. Comparative efficacy, review of benefits

Given that the strongest evidence for the comparative efficacy and tolerability of 21 antidepressants is derived from one network meta-analysis, this section will first review and summarize that publication and will then review other publications.

9.1 Network Meta-Analysis

The comparative efficacy and tolerability of antidepressants was comprehensively studied by one network meta-analysis published in February 2018 (24), a more expansive update to the same group’s original network meta-analysis published in 2009 (25). As it is the largest and most robust dataset and analysis on the topic, results from this paper form the principal argument for the inclusion of escitalopram to the essential medicines list and are summarized as follows.

The latest network meta-analysis of 522 double blinded, randomized controlled trials published from 1979 to Jan 8, 2016, comprising 116,477 participants, compared the following antidepressants to each other or to placebo for the treatment of unipolar depression: agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, vilazodone, vortioxetine, amitriptyline, clomipramine, trazodone, and nefazodone (24). The acute treatment phase was set at 8 weeks, but data from a 4-12 week treatment time period was used if the 8-week point was not available. The primary outcomes were defined as 1) efficacy - 50% reduction from baseline score on a standardized observer-rating scale for depression (for example, the Hamilton depression rating scale (HDRS) or Montgomery-Asberg depression rating scale (MADRS)), and 2) acceptability – all-cause discontinuation, which encompasses both efficacy and tolerability. Secondary outcomes were set as: final depression rating scale score, remission rate, drop-out rate due to adverse events.
Of the included 522 trials, the majority were from North America (48%, n=252) and Europe (11%, n=59). However, 37 trials (7%) recruited patients from Asia, 59 (11%) from cross-continental areas, and 34 (7%) from other or unspecified regions. The vast majority of patients, from 464 (89%) trials, had moderate-to-severe major depressive disorder, quantified as a mean reported baseline HDRS 17-item score of 25.7. It is worthwhile noting that the majority, 409 (78%) trials, were funded by pharmaceutical companies. Forty-two trials compared escitalopram to placebo or another comparator.

As per the initial study protocol, the primary analysis was derived from the 474 studies (encompassing 106,966 participants) that compared medications at dosages within the licensed range approved by US and/or European regulatory agencies. Figure 1 is a summary analysis of 432 RCTs (total n=102,443) for the efficacy figure and 422 RCTs (total n=99,787) for the acceptability figure. Escitalopram carries a modest effect size, odds ratio of 1.68 with a relatively narrow 95% credible interval (CrI) of 1.50, 1.87, while conferring a non-significantly improved drop-out rate compared to placebo (OR 0.90, 95% CrI 0.80, 1.02). Secondary outcome data for remission (OR 1.64, 95% CrI 1.47, 1.83) and drop-out rate (OR 1.72, 95% CrI 1.38, 2.14), in the supplementary material, are shown in Figure 2.

The authors estimated the median heterogeneity variance for efficacy at 0.044 (95% CrI 0.028–0.063) and 0.040 (0.023–0.062) for acceptability, suggesting moderate-to-low heterogeneity on both accounts. Per subgroup meta-regression analyses, the strongest explanation for this was the inclusion of placebo. When placebo-controlled trials were excluded, heterogeneity variance was reduced by 24% for response and 45% for dropout. Other subgroup analyses revealed...
that smaller and older studies were more likely to find larger effect sizes for the active drug against placebo, particularly in trials involving amitriptyline, bupropion, fluoxetine, and reboxetine. The authors determined risk of bias as high in 46 (9%) of 522 trials, moderate in 380 (73%) trials, and low in 96 (18%) trials.

Figure 3 presents data for efficacy and acceptability derived from 194 head-to-head trials of licensed doses of two or more active compounds. The figure incorporates GRADE evidence, with moderate levels of certainty for most of the comparisons involving escitalopram, agomelatine, citalopram, and mirtazapine. Trials involving vortioxetine, amitriptyline, clomipramine, bupropion, and nefazodone had low to very low levels of certainty. Significant findings are bolded and underlined. For the efficacy data, the agent identified by the column is superior if the odds ratio is greater than 1. If the odds ratio is less than 1 in the acceptability data, the first drug in alphabetical order is favored. Escitalopram thereby has moderate level GRADE evidence of superiority in terms of efficacy over citalopram, clomipramine, fluoxetine, fluvoxamine, reboxetine, and trazodone, making it the agent with statistically significant superiority over the most other alternative agent amongst these 21 drugs. In comparison to members of its class, SSRIs, on measures of efficacy, escitalopram appears to be non-statistically significantly superior to paroxetine (OR 1.12, 95% CI 0.93-1.35) and sertraline (OR 1.20, 95% CI 0.97-1.48). With respect to acceptability, escitalopram demonstrates moderate level GRADE evidence of superiority to duloxetine, clomipramine, amitriptyline, fluvoxamine, reboxetine, and venlafaxine. No drug was found to be more statistically significantly efficacious or better tolerated than escitalopram.
The decision to specifically analyze data from double-blind, randomized head-to-head controlled trials, including unpublished data, which generally tend to include more reported adverse side effects, and the incorporation of GRADE evidence, makes the above findings quite robust. As seen by comparing Figures 1 and 3, when trials comparing active agents to placebo were included, estimated differences between drugs were smaller. Figure 4 plots these results side by side for easier visualization. The authors identify several explanations for this, including: 1) higher placebo response rates associated with the nature of studies (frequent visits, therapeutic setting, expectation that one may receive an active treatment), 2) spontaneous improvement of depression symptoms over time which thereby increase placebo response rates, 3) higher dropout rates in those receiving the active compound thinking they have received the placebo which then may underestimate treatment effect via last-observation-carried-forward approach for imputing missing data or simply not enough treatment time to see an effect, 4) bias derived from industry interest. On this last point, the authors did not find much association between industry funding and response or dropout rate, but only a few of the included trials were not funded by industry.

![Figure 3](image-url)
In conclusion, the above evidence identifies escitalopram as an agent that maximizes efficacy and acceptability within the SSRI class and appears to do so in comparison to a great number of non-SSRI treatments as well. In the context of the greater body of literature, this review is the largest and most robust by means of study design, accounting for heterogeneity and bias, to this author’s knowledge, and therefore forms the main argument for the inclusion of escitalopram to the essential medicines list.

A summary of the earlier version of this review (25) will not be included here as this review has encompassed and expanded upon those results. The remainder of the evidence presented here constitutes other Cochrane reviews, which have considerable overlap in included studies, and non-double-blind randomized controlled trials, as those were not included in this network meta-analysis.

Figure 4. Two-dimensional graphs about efficacy and acceptability in all studies (A) and head-to-head (B) studies only. Data are reported as ORs in comparison with reboxetine, which is the reference drug. Error bars are 95% CrIs. Individual drugs are represented by different coloured nodes. Desvenlafaxine, levomilnacipran, and vilazodone were not included in the head-to-head analysis because these three antidepressants had only placebo-controlled trials. ORs=odds ratios. 1=agomelatine. 2=amitriptyline. 3=bupropion. 4=citalopram. 5=clomipramine. 6=desvenlafaxine. 7=duloxetine. 8=escitalopram. 9=fluoxetine. 10=fluvoxamine. 11=levomilnacipran. 12=milnacipran. 13=mirtazapine. 14=nefazodone. 15=paroxetine. 16=reboxetine. 17=sertraline. 18=trazodone. 19=venlafaxine. 20=vilazodone. 21=vortioxetine. 22=placebo.
9.2 Cochrane Reviews
A search of the Cochrane Database for the key word “escitalopram” on 9/24/18 yielded 15 results. Seven were excluded for irrelevance to the treatment of depression.

**Escitalopram v. other antidepressants**
An analysis of 22 randomized controlled trials (RCTs) conducted prior to July 2008, encompassing approximately 4000 subjects, were included in a review of escitalopram for the treatment of depression compared to other antidepressants (26). The primary outcome was the number of subjects who responded to escitalopram as compared to another medication (including tricyclics, heterocyclics, other SSRIs, and other new antidepressants such as SNRIs), defined as a 50% reduction in a depression scale (most commonly the HAM-D, but also the MADRS or other depression scales). The intention-to-treat approach was utilized to calculate responders and remitters to treatment and the Cochrane risk-of-bias tool was applied to all included studies.

In 6 studies (n=1823) that compared response rates between escitalopram and citalopram, there was a statistically significant difference in favor of escitalopram (OR 0.67, 95% CI 0.50 to 0.89, p = 0.006), also found in remission rates (OR 0.57, 95% CI 0.36 to 0.90, p = 0.02). Three studies (n=783) that directly compared escitalopram and fluoxetine did not find a statistically significant difference in response or remission rates but did find escitalopram to be more efficacious than fluoxetine in reduction of depressive symptoms (SMD - 0.17, 95% CI - 0.32 to - 0.03, p = 0.02; 3 studies, 759 participants) from baseline. Two studies (n=784) that compared escitalopram to paroxetine, as well as two studies (n= 489) comparing escitalopram to sertraline, did not find any statistically significant differences on all of the above parameters (response rate, remission rate, mean change in baseline of depressive symptoms).

On efficacy measures comparing escitalopram to bupropion (3 studies, n=842), there were no statistically significant differences.

Three studies of 1150 participants comparing escitalopram to duloxetine found no statistically significant differences on measures of efficacy. In a maximum of 2 studies of 495 subjects, no statistically significant differences were found on efficacy between escitalopram and venlafaxine. Sensitivity analyses did not significantly change the above results.

In summary, escitalopram was clinically superior to citalopram, clinically superior to fluoxetine on one secondary outcome, and equivalent to several other antidepressants (paroxetine, sertraline, bupropion, duloxetine, and venlafaxine).

**Other antidepressants v. escitalopram**
The newer review comparing citalopram to escitalopram (27) included one additional study (28) to the above review focusing on escitalopram and concluded similar results. The authors note that the included studies were all funded by the same manufacturer of both drugs and therefore may include the possibility of “wish bias.”

A Cochrane review comparing S-adenosyl methionine (SAMe) to escitalopram (29) included just one low-quality study of 129 participants (30), which did not provide strong evidence for
any difference in terms of change in depressive symptoms from baseline to end of treatment as a monotherapy nor in terms of drop-out rates.

A Cochrane review comparing agomelatine to several other antidepressants (31), including escitalopram, identified two studies (32,33) that were not able to find evidence that agomelatine was more or less effective than escitalopram in treatment response (RR 1.05, 95% CI 0.95 to 1.16, P value 0.33, I² = 0%; two trials, 462 participants), remission rates (RR 1.13, 95% CI 0.94 to 1.35, P value 0.20, I² = 0%; two trials, 462 participants), total drop-out rates (RR 0.81, 95% CI 0.50 to 1.32, P value 0.76, I² = 0%; two trials, 462 participants), drop-out rates due to inefficacy (RR 1.34, 95% CI 0.43 to 4.21, P value 0.61, I² = 0%; two trials, 462 participants) or side effects (RR 0.40, 95% CI 0.15 to 1.06, P value 0.07; two studies, 462 participants).

A study comparing duloxetine against other antidepressants (34) was excluded because it used the same 3 studies as in the aforementioned review comparing escitalopram to other antidepressants (26).

Special populations
The Cochrane review assessing risk and benefits of antidepressant use, including escitalopram, in patients with co-morbid depression and alcohol dependence found that antidepressants were helpful in increasing alcohol abstinence during the trial and reducing number of drinks consumed on drinking days, which were robust findings when studies with high risk of bias were excluded (35). However, there was not enough data to compare different antidepressants for this use.

A Cochrane review comparing antidepressants to placebo in the treatment of depression in dementia populations found little to no difference in response as measured by scores on depression rating scales in a 12-week time period, and unlikely any after six to nine months of treatment (36). Of the 10 included studies, one of them (n=60) specifically compared escitalopram to placebo and found similar results (37).

One study was excluded as it did not have enough data to compare antidepressants in patients with end-stage kidney disease on dialysis (38).

9.3 PubMed Search
A PubMed search conducted October 2018 of “escitalopram,” “comparison,” and “depression” yielded 238 abstracts. Of these, 65 were selected for relevance to the clinical treatment of depression. An additional 39 were excluded for the following reasons: duplicates (13), no included studies looking at escitalopram alone (10), outcomes only indirectly related to depression (6), antidepressants as a switch or augmentation strategy (3), irrelevance (3), too small (1), not comparing escitalopram to a placebo or an antidepressant (1), and poor design (2).

Review articles
1) A review paper from 2009 of 16 randomized controlled trials using the MADRS or HAMD scales, published up to October 2007 (with some unpublished data), encompassing 4549 subjects (escitalopram n=2272, SSRIs n=1750, SNRIs n=527), compared escitalopram to pooled SSRIs and SNRIs after a treatment length of 8 weeks (39). The primary outcome was set at mean treatment difference and secondary outcomes were defined as response rate (50% reduction in...
MADRS from baseline) and remission rate (MADRS total score ≤ 12). The denominator of all outcomes was set to be all patients who received at least one dose of the study medication (n=4549), rather than all randomized patients (n=4602). While this may amplify results, as the denominator is slightly smaller than the overall study population, it is likely a more accurate measure of effect of study drug since it guarantees that participants actually did receive the study medication. Separate analyses were conducted for escitalopram against all comparators, against SSRIs, against SNRIs, and against placebo. Sensitivity analyses looking at the effect of trial length and dose effect were also conducted.

Of the 16 included trials, 14 trials were included in Cipriani et al. 2018 network meta-analysis, one was not (40), and one was Forest Laboratory data that could not be specifically located in the reference list. Using data from all 16 trials, the authors estimated a small but significant mean treatment difference of 1.1 points on the MADRS (95% CI: [0.6, 1.6], p < 0.0001) in favor of escitalopram against all other comparators. With respect to response rate of escitalopram against all other comparators, the odds ratio was 1.33 (95% CI: [1.15, 1.53], p < 0.0001), with similar effect size for remission: OR 1.22, 95% CI: [1.06, 1.40], p = 0.0059.

The overall mean difference in treatment effect was very small, at 0.9 points (95% CI: [0.3, 1.5], p=0.0023), but statistically significantly greater among patients treated with escitalopram compared to the SSRIs (citalopram, fluoxetine, paroxetine, and sertraline). Response rate effect was modest and statistically significant (OR 1.24 (95% CI: [1.06, 1.46], p=0.0089) though remission rates did not significantly differ.

Against SNRIs ( duloxetine and venlafaxine), the estimated mean treatment difference was higher for escitalopram at 1.7 points (95% CI: [0.5, 2.8], p=0.0038), with a higher response difference (OR 1.63, 95% CI: [1.23, 2.16], p=0.0007) and remission rate (OR 1.45, 95% CI: [1.10, 1.92], p=0.0038).

The effect of escitalopram was largest in comparison to placebo (data from 5 trials), with an estimated mean treatment difference of 2.3 MADRS points (95% CI: [1.4, 3.1], p < 0.0001).

Per sensitivity analyses, the mean treatment difference from four trials with longer study durations (roughly 6 months) was modestly higher at 1.7 points (95%CI: [0.7, 2.6], p = 0.0005) for all patients by the end of study period. The estimate at week 8, in those same studies, was comparable to the above results at 1.1 points (95%CI: [0.2, 1.9], p = 0.0123). Five studies that looked at a higher dose of escitalopram at 20 mg found a higher mean treatment difference of 2.0 points (95% CI: [1.1, 3.0], p < 0.0001).

The withdrawal rate due to adverse events was 5.4% for escitalopram and 7.9% for all comparators (p=0.0007) which was primarily driven by significantly higher attrition rates in the SNRI group (5.3% vs. 12.9%, p<0.0001), as the comparison to SSRIs was insignificant (5.4% vs. 6.3%, p=0.2243). The total withdrawal rate was similar for SSRIs and for SNRIs as withdrawal rate for adverse events.
All in all, escitalopram had a modest and significant advantage over pooled SSRIs and a somewhat larger advantage over pooled SNRI data. Escitalopram appears to be considerably more tolerable than the SNRIs.

2) A small review article of two double blinded trials (41), both of which were included in Cipriani et al. 2018 (24), involving 491 participants studied treatment response and remission differences between escitalopram and venlafaxine, finding a non-significant difference in treatment response (OR 0.81 (95% CI 0.54, 1.22)) and remission (OR 0.90 (0.61, 1.34)) by the end of a 7-8 week treatment period. This study was funded by Wyeth Pharmaceuticals, the maker of venlafaxine.

3) A somewhat larger study analyzed four double blinded, placebo-controlled trials (42), encompassing 1140 participants from the US with major depressive disorder, that used the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the MADRS for assessment. After 8 weeks of treatment with escitalopram, 34% of the patient population achieved Q-LES-Q scores within 10% of population norm as compared to 27% of those taking placebo. There was a modest but significantly greater improvement in quality of life enjoyment and satisfaction after 8 weeks of treatment with escitalopram (from 37.5±7.9 to 46.6±9.9) than with placebo (from 37.3±7.8 to 44.2±10.6) (P<0.001, t value=4.05, d.f.=830). This study did not compare change in MADRS score, treatment response or remission as measured by MADRS, in the escitalopram arm compared to placebo arm.

4) An analysis of claims data from 2003-2005 of geriatric clients of the Health Care Information Solutions (IHCIS) National Managed Care database, which includes medical and pharmacy claims of over 25 million clients of over 35 health insurance plans from all census regions of the United States (43). Endpoints included treatment persistence and hospitalization utilization, but not treatment response or remission as measured by a depression rating scale. The study identified 459 clients who received escitalopram against 1517 clients who received other SSRIs/SNRIs over a 6-month treatment period. At baseline, escitalopram users were significantly more likely to have comorbid generalized anxiety disorder (GAD), higher number of baseline prescription drugs, higher mean prescription drug costs, and higher mean total healthcare costs. Escitalopram users were less likely to discontinue their treatment as compared to those on SSRI/SNRI using Chi-square testing (60.78 vs. 65.85%, p=0.047), which remained significant after adjustment for baseline differences (Hazard Ratio 0.85, p=0.012). Time to index therapy discontinuation, measured by Kaplan-Meier estimation, was also significantly longer in patients treated with escitalopram, with a median time of 101 days for those on escitalopram and 92 days for those on an SSRI/SNRI (p=0.003). Though rate of hospitalization did not differ between the two groups in the unadjusted nor adjusted analysis, the escitalopram group appreciated 39% fewer hospitalization days, a significant finding only in the adjusted analysis (p=0.004). Though the study did not compare treatment response or remission rates using a depression rating scale, escitalopram users appeared to adhere to treatment longer, suggesting better tolerability in this naturalistic, retrospective analysis.

The major limitation of this study is the use of pooled data, which obscures medications to which escitalopram may be inferior or equivalent. For example, a meta-analysis comparing escitalopram to SSRIs and SNRIs separately found a significantly higher discontinuation rate for
those on SNRIs but not for those on SSRIs, which drove an overall higher discontinuation rate for the pooled SSRI/SNRI data (39). The results here may hide a similar effect.

A study by the same group did compare escitalopram users to specifically citalopram users with similar methodology (44), finding that compared to those treated with citalopram (n=232), clients taking escitalopram (n=459) were less likely to discontinue treatment (hazard ratio [HR]=0.83, p=0.049) or switch to another second generation antidepressant (HR=0.62, p=0.001). No other head-to-head trials were found.

5) A more recent study from 2011 analyzed pooled data from three randomized, double-blind, multicenter trials from the US, comparing escitalopram (n=462) to an SNRI (n=467), duloxetine or venlafaxine (45). Escitalopram treatment was associated with 41% higher odds of depression remission at week 8 compared to SNRI treatment (p=0.0096). The study also found that 41.6% of escitalopram treated patients compared to 48.0% of SNRI-treated patients experienced adverse effects during the study period (p=0.0496). This study was funded by Forest Research Institute.

6) A study that aimed to compare vortioxetine to a variety of different antidepressants, including escitalopram, used effect sizes of study drug against placebo from “pivotal short-term double-blind trials for vortioxetine and from publicly available sources for the pivotal short-term double-blind trials” for other antidepressants as an indirect comparison (46). Efficacy outcomes were set as response (50% reduction from baseline) as measured by MADRS or HDRS and the tolerability outcome was discontinuation due to an adverse event, all over a 6-10 week treatment period with preference for the 8-week timepoint. Three studies and additional data from Lundbeck were included.

The response rate calculated for the pooled data for escitalopram was 53.1% as compared to 38.1% for placebo, a risk difference of 0.150 with 95% CI (0.091-0.209) with number needed to treat (NNT) of 7 participants (95% CI: 5–11). The calculated risk difference and 95% CIs for other drugs (vortioxetine, duloxetine, vilazodone, levomilnacipran, venlafaxine, and sertraline) substantially overlapped with that of escitalopram. Discontinuation due to an adverse rate was observed to be 5.2% in those on escitalopram as compared to 1.9% in the placebo group, with a risk difference of 0.033 (95% CI: 0.011-0.054) and a number needed to harm (NNH) of 31 (95% CI: 19-92). Here, the confidence intervals did not overlap with that calculated for sertraline (risk difference 0.154, 95% CI (0.090-0.219)) nor venlafaxine (risk difference 0.128, 95% CI (0.092-0.164), suggesting that perhaps escitalopram is more favorable with respect to discontinuation rate due to adverse events. Given that the confidence intervals for NNT and NNH did not overlap, it is unlikely that response and discontinuation due to adverse event are equally likely. No statistical tests were done to compare these values.

In an effort to weigh the likelihood of response to the likelihood of discontinuation due to adverse event, the authors calculated the likelihood to be helped or harmed (LHH) as measured by the ratio of NNH to NNT. If LHH is >1.0, the patient is more likely to appreciate the response. Escitalopram, with an LHH of 4.6 ranked second to vortioxetine (5.1), appeared similar to duloxetine (4.3) and more substantially superior to vilazodone (3.30), levomilnacipran (1.8), venlafaxine (1.4), and sertraline (1.2). No statistical tests were done to compare these
values. Notably, the pooled vortioxetine data amassed a total of 3008 patients, about 5 times more than the total number of escitalopram patients (n=599). Unequal patient pool sizes may explain some of the noted difference. Funding of this study was supported by Lundbeck.

**Double-blinded RCTs**

One double-blinded, randomized controlled trial was identified that was not included in the 2018 network meta-analysis (24) because it was published after January 2016 (47). In this 12-week Romanian study of 287 participants randomized to either escitalopram or agomelatine, both agents demonstrated significant improvement in the 17-item HDRS as compared to baseline but no significant difference between groups. No funding sources were disclosed.

**Single-blinded, non-randomized trials**

A Taiwanese study of 302 patients were assigned to either escitalopram or paroxetine, based on clinical judgment, in this single-blinded study for a treatment course of 8 weeks (48). Raters on the scale of choice, the 21-item HAM-D, were blinded to the patients’ diagnoses and study medications. The mean change in HAM-D21 was significantly more for escitalopram than paroxetine at week 6 (-11.8 vs. -10.4 points) and 8 (-13.0 vs. -11.5 points respectively). Response rates were also significantly different at 67.5% in the escitalopram group compared to 55.9% in the paroxetine group (p<0.05 in both unadjusted and adjusted models for baseline HAM-D scores) by the end of 8 weeks. Remission rates were not significantly different. The paroxetine group was more likely to have adverse effects such as weakness (P<0.01), nausea and vomiting (P<0.001), drowsiness (P<0.01), somnolence (P<0.01), and decreased appetite (P<0.05). This was a non-industry funded study.

**Open-label RCTs**

Four studies comparing escitalopram to various other agents were open-label and randomized in design. The largest study, an international study of 1008 patients, aimed to study differences in cognitive performance between antidepressant groups and placebo (49). 1008 depressed patients and 336 healthy controls were randomized to either escitalopram, sertraline, or venlafaxine (336 participants in each group). Over an 8-week period of treatment and repeated cognitive testing, no change in cognition was found over time, testing, or treatment for any of the studied medications.

A study of comparison between escitalopram as monotherapy and combination therapy, with and without escitalopram, randomized 605 participants to escitalopram+placebo, bupropion+escitalopram, and venlafaxine+mirtazapine such that the first medication in each pair was open-label and the second medication was blinded to the participant (50). No significant differences between groups were found with respect to remission or response rates as measured by the QIDS-SR16 at neither 12 nor 28 weeks.

Finally, two small studies from India compared escitalopram to desvenlafaxine (51) and agomelatine (52) in an open-label, randomized trial. The first study randomized 60 patients to either escitalopram or desvenlafaxine and found that both arms demonstrated significantly reduced HAM-D, HAM-A, and CGI scores from baseline but did not find significant between-group differences on these measures (51) at the end of 6 weeks. The second study randomized 64 patients to escitalopram or agomelatine and compared group differences at the end of a 24-week
treatment period (52). 100% of patients exhibited a response (>=50% reduction in HAM-D17) in both groups, with a significantly lower mean HAM-D17 score in the escitalopram group (4.41) than in agomelatine group (5.87), though this is unlikely to be clinically meaningful as remission was defined as scores <=7. No statistically significant differences with respect to adverse events was found between groups. The open-label design with no placebo control makes it unlikely that this study would find significant, meaningful differences between the two drugs.

**Observational**

One Spanish observational, multicenter, retrospective study conducted using computerized medical records gathered data from 965 patients taking escitalopram (n=131), citalopram (n=491), or venlafaxine (n=343) between 2003-2007 with a follow-up period of at least 18 months. The authors defined remission as completion of 6 months of pharmacotherapy and found that the concordance of this proxy measurement with documentation of remission (undefined) per chart review in a random sampling yielded 91.7%. Since it is not clear how remission was documented in the chart, the meaning of this concordance measurement, and therefore the validity of the authors’ proxy measurement of remission as completion of 6 months of pharmacotherapy, is unclear. The authors found that escitalopram-treated patients achieved higher remission rates compared to citalopram (58.0% vs. 38.3%) and venlafaxine-treated patients (32.4%), p < 0.001. However, the escitalopram group at baseline was younger, male-dominated, with less co-morbidity compared to the other two groups. The study did not attempt to correct for these baseline differences before assessing for statistical significance between different remission rates. This study was funded by Lundbeck.

**Expert opinion**

Finally, an expert consensus meeting was held in 2007, funded by Lundbeck, in which depression experts from multiple countries amassed published evidence from randomized controlled trials and meta-analyses, designating fair comparison RCTs as "Class A" evidence and meta-analyses as "Class B" evidence, given post hoc design such that the data generates the hypothesis rather than confirms it. The authors define “definite superiority” of a medication if there is evidence of its superiority on the primary efficacy measure from two pivotal studies under conditions of fair comparison at approved doses of the studied medications or if there is one such pivotal study supported consistently by meta-analyses. It is not clear from the article what constitutes a “fair comparison.” The authors specifically looked at clomipramine, duloxetine, escitalopram, milnacipran, mirtazapine, and venlafaxine “on the basis of published claims” that they may be superior in efficacy to other medications.

Several variables were taken into consideration when determining the quality of the study: the validity of the outcome variable (ex. change in depression scale scores), the usefulness of reported clinical measures like response and remission, the statistical methods, the time course of response, the decision to pool data as opposed to conducting meta-analyses, and breakdown of subtypes or subgroups of patients.

Relevant to escitalopram, the authors identified two fair comparison RCTs, “Class A evidence” in favor of 20 mg escitalopram over 40 mg citalopram (53) and over 40 mg paroxetine (54), both of which were included in Cipriani et al. 2018 meta-analysis (24) and Kennedy et. al 2009 (39) reviewed earlier in this section. The article also identified several meta-analyses, or “Class B”
evidence, that favored escitalopram over citalopram (55–57). Finally, they identified the aforementioned meta-analysis by Kennedy, et al. (39) as reasonable Class B evidence in favor of escitalopram over all comparators tested. Given the above criteria, the article identified escitalopram, clomipramine, and venlafaxine as being of "definite superior efficacy" in treatment of moderate-to-severe depression.

The overall merit of this study is uncertain, given that the meeting itself was funded by Lundbeck, the pharmaceutical company behind branded escitalopram, and given somewhat arbitrary criteria for the designation of “definite superior efficacy.” Additionally, no statistical methodology was involved in this publication. However, this article does represent the expert consensus on the treatment of depression.

**SUMMARY**

In summary, the bulk of the argument in favor of escitalopram as an efficacious treatment for depression over several other available agents, is derived from a major, network meta-analysis of 522 randomized controlled trials incorporating GRADE evidence, that designates escitalopram as a highly performing drug both on measures of efficacy and tolerability (24). The issue of tolerability is particularly important as antidepressants take several weeks to take maximal effect; thus a more tolerable drug is more likely to be adhered to long enough to witness an antidepressant effect. On measures of efficacy in head-to-head trials as compared to members of its class, SSRIs, escitalopram appears to be statistically significantly superior to citalopram, fluoxetine, and fluvoxamine, and non-statistically significantly superior to paroxetine and sertraline. With respect to acceptability, escitalopram appears to be statistically significantly superior to fluvoxamine and non-statistically significantly superior to all others.

A meta-analysis by the same group looking at escitalopram compared to other agents largely confirmed those findings, and provided more detail about specific adverse events (26). Escitalopram was generally a very well tolerated drug, appearing equally or, in the case of bupropion, sertraline, and duloxetine, less likely to experience side effects.

Other review articles by different authors (39,41), but of RCTs included in Cipriani et al. 2018 (24), confirmed similar results of escitalopram superiority on measures of efficacy and drop-out rates, particularly in comparison to SNRIs.

Other forms of evidence, including retrospective analyses of claims data (44,58), single-blinded trials allocating patients to treatment by clinical judgment (48), open-label randomized trials (49–52), and retrospective, observational data (59) either found statistically significant benefit to escitalopram on a variety of measures, including response and remission rates and likelihood of treatment withdrawal, or equivalence to comparators. One paper delineating expert consensus was also support the superiority of escitalopram over other antidepressants (60). Of note, none of the references found superiority of another drug over escitalopram, including articles that had funding from the comparator pharmaceutical agency, which may introduce bias in favor of the comparator.

In conclusion, escitalopram demonstrates high performance on measures of efficacy and tolerability that is at best superior to most other available antidepressants and at worst, equivalent
to several available antidepressants. The body of evidence supporting this notion is robust, not only from very large network meta-analysis of double blinded randomized controlled trials, but also from other data sources as aforementioned.
10. Summary of comparative evidence on escitalopram safety

A systematic review was conducted using Cochrane and PubMed databases (last search November 2018). The keyword “escitalopram” was used for the Cochrane search. The keywords “escitalopram” and “safety” were used for the PubMed search. There were no language requirements.

The initial search yielded 15 reviews in Cochrane and 422 abstracts (including Cochrane reviews) in PubMed. The abstracts were narrowed down to 368 based on publication date; articles published prior to 2002 (year of escitalopram FDA approval) were excluded considering they would have been considered in the FDA approval process and then subsequent Cochrane reviews. After excluding irrelevant article types (i.e. interview, personal narrative, etc.), 194 abstracts remained and were reviewed. Of those 194 abstracts, 122 were excluded for limited relevance in evaluating escitalopram comparative safety (i.e. primarily comparative study for citalopram without evaluating escitalopram or did not comment adequately on safety), inadequate sample size, study design of insufficient quality, and/or data availability limitations. Of note, an additional 12 publications that were identified by hand-search and reference-checking were included in the safety evaluation. As a result, 40 published works are considered in the escitalopram safety assessment below (with a smaller proportion directly cited in the main text).

10.1 Estimate of Total Patient Exposure to Date

The United States Food and Drug Administration first approved escitalopram for use in patients in August 2002 (61). No data are currently available for worldwide total exposure to escitalopram. In the US, mental health prescriptions are in the top 3 of all prescriptions, increasing from just over 300 million in 2012 to nearly 400 million dispensed prescriptions in 2016 (62). Regarding specific prescribing for escitalopram, from 2006-2016, the number of US prescriptions have ranged from just under 17 million (2013) to nearly 27.5 million (2006) per year, including approximately 25.2 million in 2016 and achieving a ranking of 26th of all prescribed medications in the US (13). Also, escitalopram is one of the most commonly prescribed antidepressant medications (often in the top 5 annually) in the United States (13).

To get a better sense of global patient use, a number of retrospective international articles on usage trends were reviewed. An article on prescription patterns of antidepressants in five tertiary care psychiatric centers in India (n = 312 patients) noted that the majority of patients were prescribed SSRIs (n = 194), with the caveat that many were for non-depression diagnoses, and that escitalopram (n = 114) was the most commonly used medication (63). Another study from India on prescribing patterns at 11 centers (n = 4480 patients) found that the most commonly prescribed antidepressant was escitalopram (n = 951 of 2816 patients on antidepressants) (17). An article on antidepressant prescriptions in children and adolescents in China treated at 40 psychiatric centers (n = 109 patients) indicated that escitalopram (n = 14 patients), sertraline (n=24), and fluoxetine (n = 41) were the most commonly prescribed antidepressants (64). In another study of Asian patients (n = 370), escitalopram and mirtazapine (20% each) were the most commonly prescribed antidepressants for patients with a medical co-morbidity (65). In a study on SSRI and SNRI use in Italy from 2003-2009 (n = nearly 1,000,000 patients), escitalopram had the greatest increase in prevalence of use (nearly 3% increase) and highest
frequency of participants on antidepressants with good adherence to their medication regimen (28.5%) (66). In a study on prescribing patterns for antidepressants in Italian primary care, SSRIs, particularly escitalopram (n = 253 on escitalopram out of 1377 total), were the most commonly prescribed antidepressant medications (67). In a Danish study evaluating prescribing patterns in 2009-2010, escitalopram was more commonly chosen as the first SSRI over citalopram and sertraline (n = 65,313 prescriptions for treatment-naïve patients, 19% of which were for escitalopram with higher rates when psychiatrists and hospital physicians were the prescribers) (22). These studies indicate the international popularity of escitalopram.

10.2 Common Adverse Effects and Frequency Estimates (68–70)
The most common side effects (per epocrates (69), affecting at least 2% of people on escitalopram at recommended doses) include headache, nausea, sexual dysfunction (ejaculatory dysfunction, decreased libido, anorgasmia, and impotence), sleep disruption (somnolence, insomnia, abnormal dreams, yawning, and daytime sedation), xerostomia, gastrointestinal disruption (diarrhea, constipation, anorexia, increased appetite, vomiting, dyspepsia, and abdominal pain), fatigue, diaphoresis, dizziness, flu-like syndrome, menstrual disorder, paresthesia, rhinorrhea, sneezing, blurred vision, rash or itching, tremor, and emotional blunting.

Serious side effects include suicidality, worsening depression, (hypo)manic conversion, cardiac effects (QT prolongation and torsades de pointes), serotonin syndrome, hematologic changes (abnormal bleeding and altered platelet function), allergic reactions (anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis), acute-closure glaucoma, seizures, hyponatremia, priapism, extrapyramidal symptoms and withdrawal symptoms in the event of abrupt discontinuation.

Depression

Comparison with other SSRIs
In a Cochrane review comparing escitalopram to other antidepressant medications in major depressive disorder, fourteen multicenter, randomized control trials (RCTs) with double-blinding compared escitalopram to another SSRI (n = mean of 280 subjects/study with range of 30-459) (26). They demonstrated that escitalopram did not have significantly different rates of mild to severe adverse events than citalopram (n = 1802 in 6 RCTs), fluoxetine (n = 804 in 4 RCTs), or paroxetine (n = 784 in 2 RCTs). Also, there was no significant difference in serious adverse events for escitalopram compared to sertraline (n = 483 in 2 RCTs); however, escitalopram had a decreased incidence of diarrhea. Of note, a limitation of this review is that the majority of the included studies failed to fully describe the allocation process, although they appeared to have similarities in their design and conduct. Unless otherwise noted above, escitalopram and other SSRIs had similar rates of agitation, anxiety, constipation, diarrhea, dry mouth, hypotension, insomnia, nausea, urinary complaints, drowsiness, vomiting, deaths, suicide, suicidality, and other adverse events (such as jitteriness, fatigue, flu-like syndrome, headache, impotence, decreased libido, pain, and increased sweating or yawning).

In a more recent systematic review and network meta-analysis of double-blinded RCTs in major depression (n = 116,447 patients, 522 RCTs between 1979-2016) comparing 21 antidepressants or placebo, escitalopram (moderate evidence grade) was among the most tolerated
antidepressants according to low drop-out rates for participants taking escitalopram (24). The other similarly well tolerated SSRIs included citalopram, fluoxetine, and sertraline. Also providing evidence of escitalopram tolerability, retrospective claims analysis of antidepressant persistence from 2002-2005 in the US (n = 43,921) demonstrated that people who had started on escitalopram (compared to citalopram, fluoxetine, and paroxetine) were more likely to have continued the medication and less likely to require augmentation at 2 and 6 months of treatment (71).

In an older review of RCTs from before 2007 (n = >4000 escitalopram treated patients), none of the escitalopram-treated patients attempted suicide or had higher suicidal behavior or thoughts than placebo (72). Also, while escitalopram had higher sexual dysfunction adverse events than paroxetine, it was comparable to citalopram.

Escitalopram has a fairly similar side effect profile to its closely related citalopram based on multiple studies, including a French RCT performed in the primary care setting (n = 357) (73) and a multicenter Chinese RCT (n = 240) (28). Of note, an open-label pilot study on escitalopram doses up to 50 mg in patients who had not responded to adequate citalopram treatment (n = 42), there was no increase in serious adverse events, while there was a dose-related decrease in tolerability (increased headache, nausea, diarrhea, and nasopharyngitis) for doses higher than the typically prescribed 10-20 mg (74).

Comparison with other classes of antidepressant medications
In a Cochrane review comparing escitalopram to other antidepressant medications in major depressive disorder, eight RCTs compared escitalopram to newer antidepressant medications (i.e. SNRIs; n = mean of 307 subjects/study with range of 202-547) (26). Regarding serious adverse events, there was no significant difference between escitalopram and bupropion (n = 822 in 3 RCTs), duloxetine (n = 1111 in 3 RCTs), or venlafaxine (n = 487 in 2 RCTs). Regarding mild to moderate adverse events, escitalopram was associated with lower rates of constipation (n = 557 in 2 RCTs), dry mouth, and insomnia (n = 822) and a higher rate of fatigue and yawning (n = 557) than bupropion; less dry mouth, nausea, and dizziness (n = 1111) compared to duloxetine; and lower rates of nausea and sweating than venlafaxine (n = 487). The incidence for other mild to moderate side effects were comparable between escitalopram and the other newer antidepressants.

In a more recent systematic review and network meta-analysis of double-blinded RCTs in major depression (n = 116,447 patients, 522 RCTs between 1979-2016) comparing 21 antidepressants or placebo, as noted above, escitalopram (moderate evidence grade) was among the most tolerated antidepressants (24). The other similarly well tolerated newer antidepressants included agomelatine and vortioxetine; by contrast, amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine were among the most poorly tolerated antidepressants based on their high drop-out rates.

In a multicenter (29 sites), double-blind, randomized Romanian study (n = 417) comparing agomelatine with escitalopram, there were overall similar incidences of adverse events, though escitalopram was associated with higher levels of gastrointestinal disturbance (nausea, vomiting, abdominal pain, and diarrhea) (47).
Comparison with placebo
In a Cochrane review comparing escitalopram to other antidepressant medications in major depressive disorder, nine RCTs included comparisons with placebo; however, the focus of the review was on comparison between active medications and did not include detailed placebo analysis (26).

In 2011, the FDA announced high doses of citalopram could prolong the QT interval; subsequently, the European Medicines Agency also issued an alert for escitalopram. In an Italian observation study of 35 psychiatric services over a 3-month period (n = 426 patients), citalopram increased the QTc, while escitalopram did not significantly increase the QTc (75). Although the cross-sectional study design has limitations, the evaluated measures were objective and supported by multiple centers. In a large (n = 3298), double-blind placebo-controlled RCT study of escitalopram’s cardiovascular toxicity profile, escitalopram affected heart rate without significantly altering other cardiologic parameters or increasing cardiac-associated adverse events (76).

In a placebo-controlled, double-blinded RCT on escitalopram use in heart failure patients (n = 372) over a median time of > 18 months, there was no difference in serious adverse effects, except that the placebo group had higher rates of worsening depression. Also, there were slightly higher dropout rates in the escitalopram group, usually occurring within the first 6 weeks (77). In two placebo-controlled RCTs evaluating escitalopram use in acute coronary syndrome patients (n = 217 (78) and n = 240 (79)), there was no difference in serious adverse events or major safety measures with escitalopram treatment, although the first study had slightly higher rates of dizziness with escitalopram treatment.

In double-blind, placebo-controlled RCTs of chronic hepatitis C patients with interferon-alpha/ribavirin-associated depression (n = 389 in 3 RCTs), the escitalopram group had fewer respiratory problems and a higher rate of dizziness; otherwise, there were no major differences in the side effect profiles (80). In a multicenter (21 hospitals in Germany), double-blind placebo-controlled RCT on depression in HCV patients (n = 181 patients without a prior psychiatric history) undergoing IFN treatment, there was no difference in the tolerability and safety between the groups beyond a slightly higher incidence of adverse events in the placebo group (81).

Anxiety
Escitalopram was approved by the FDA for use in generalized anxiety disorder in December 2003.

In a 2011 meta-analysis of 3 RCTs (n = 1388) (82) and a 2005 older pooled results analysis of 3 similarly designed double-blind RCTs (n = 850) (83) comparing escitalopram versus placebo in generalized anxiety disorder, escitalopram had significantly higher rates of anorgasmia, fatigue, and diarrhea in the meta-analysis with the addition of increased nausea, ejaculation disorder (in males), decreased libido, and insomnia in the pooled results analysis.
In a more recent meta-analysis of three placebo-controlled RCTs (n = 1598) on escitalopram use in social anxiety disorder, the overall withdrawal rates (often for mild to moderate adverse events) were higher for escitalopram than placebo, though the withdrawal rates were more comparable in a flexible dose study (84).

In a double-blind RCT comparing escitalopram, citalopram, and placebo use in panic disorder (n = 366), adverse events in the escitalopram and placebo groups were comparable (85).

**Special populations**

**Children and adolescents**
In a 2018 review of RCTs published on antidepressant use in depressed pediatric patients, 7 RCTs were identified, 2 of which compared escitalopram to placebo (n = 312 in an acute-phase study and 165 in an extension study) (86). While there have been concerns about the potential for increased suicidality with SSRI treatment, neither RCT found an increase in suicidality with escitalopram. The most common side effects were generally rated as mild/moderate and were of a similar type to those reported for adults.

In a placebo-controlled, double-blinded RCT of escitalopram treatment for pediatric depression (n = 268), the escitalopram rates of adverse events were similar to placebo (87).

In a retrospective, new-user cohort study based on paid health insurance claim data (1997-2009, n = 11,3714 on SSRIs out of 50 million covered patients) provided by an IMS unit, Lifelink (88), escitalopram and citalopram had the highest crude incidence of ventricular arrhythmia, cardiac arrest, or sudden cardiac death, while fluoxetine had the lowest incidence. Of note, these events were fairly rare (total of 40 for all subjects).

**Pregnant and lactating women**
A 2012 review evaluated escitalopram use in pregnancy and breastfeeding, which included data from 5 cohort studies (2 prospective and 3 retrospective), 1 case-control study, and 5 case-reports (89). Four studies reported on major malformations with escitalopram use, which had incidence rates that were within the range for the general population. One prospective cohort study reported an increase in perinatal complications (lower live birth rates, low birth weight infants, and higher rates of spontaneous abortion) compared to placebo, albeit with no difference compared to other antidepressants. Regarding safety in breastfeeding, no adverse events have been reported for the fewer than 50 exposed cases reported in the literature at the time of the review. Overall, few studies have focused on the escitalopram safety profile during these life events and the studies included in this review have significant design heterogeneity while none satisfied the recommended methodological criteria for assessing teratogenicity of drugs.

Based on a 2015 review of SSRI use during breastfeeding, there are limited data on escitalopram safety in the postpartum period (n = 8 publications, some case reports, on 37 neonates) (90). Only one neonate was reported to have a serious adverse event, necrotizing enterocolitis at day 5 of life. Of note, based on a total of 22 studies for sertraline (n = 279 cases, including one RCT), sertraline (along with paroxetine) is recommended for using during breastfeeding, while fluoxetine, citalopram, and duloxetine are not recommended as first-line therapy.
**Geriatric and aging population**

With consideration of the problematic risk of falls in the elderly, a network meta-analysis compared the chance of an adverse event (dizziness) that could increase fall risk with various antidepressants (n = 4588), which included escitalopram in two of the fifteen studies (91). While duloxetine and venlafaxine had high risks of increasing dizziness, escitalopram carried an intermediate risk (comparable with citalopram and paroxetine) that was slightly higher than that for sertraline and fluoxetine.

In an extension study of a placebo-controlled RCT evaluating escitalopram in elderly patients (n = 225), the most common adverse events with escitalopram were accidental injury, rhinitis, increase in weight, and arthralgia (92). A major limitation of this extension study is that it lacked a placebo group and the common adverse events observed with escitalopram probably also have a non-zero incidence in elderly patients.

In a randomized, placebo-controlled trial of elderly patients with generalized anxiety disorder (n = 177), patients taking escitalopram had higher rates of fatigue, somnolence, and urinary symptoms; of note, the greatest difference in adverse event reporting between escitalopram and placebo was in the week when the escitalopram dose was doubled (93).

**SUMMARY**

Based on the evidence above, escitalopram is at least as safe, if not safer, than amitriptyline and fluoxetine. Based on a 2018 systematic review and network meta-analysis of 522 RCTs, escitalopram is among the most-tolerated antidepressant medications. It was comparable to fluoxetine, but much more tolerated than amitriptyline. Furthermore, it is internationally popular with high reported adherence rates in countries like Italy. Escitalopram has a similar side effect profile to many other SSRIs when studied in depression and anxiety, including gastrointestinal symptoms and sexual dysfunction, which are often rated as mild to moderate and are not known to increase morbidity or mortality.

Regarding more serious adverse events, there has been concern about QTc prolongation with citalopram that was also sometimes applied to escitalopram, especially in Europe. In the pediatric population, there was a higher rate of cardiac events with escitalopram than placebo with the caveat that cardiac events were a very rare occurrence in this population. There is even greater support in the literature that escitalopram is well-tolerated from a cardiovascular perspective, including in patients with recent acute coronary syndrome, heart failure, and chronic hepatitis diagnoses.

With respect to special populations, escitalopram and placebo treatment do not have any difference in suicidality in the pediatric population. While there are limited data in pregnant and breastfeeding patients with significant limitations in study design and sample sizes, escitalopram has been fairly safe in that population. For geriatric patients, a major concern is the reported increase in dizziness, which has also been observed in younger patients. However, the dizziness increase is only an intermediate increase based on network meta-analysis (lower than SNRIs, higher than sertraline and fluoxetine, and comparable to other SSRIs). More importantly, there
has been no reported increase in serious adverse events with escitalopram treatment in geriatric patients.

**Additionally relevant references not cited in main text**


11. Comparative cost and cost-effectiveness

11.1 Comparative cost

As cost information was not available through the *International Medical Products Price Guide*\(^1\), managed by Management Sciences for Health (MSH), drug pricing was obtained manually through search of WHO’s list of price sources\(^2\) and personal contact with all suppliers listed in the MSH guide\(^3\). Listed costs are in the original country currency for the package listed. Exchange rates to U.S. Dollars (USD) were calculated manually with rates as updated as October 2018. The cited links were all last accessed in November 2018.

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\(^3\) [http://mshpriceguide.org/en/list-of-addresses/?menuNo=16](http://mshpriceguide.org/en/list-of-addresses/?menuNo=16)
\(^7\) [https://www.medicinpriser.dk/default.aspx?lng=2](https://www.medicinpriser.dk/default.aspx?lng=2)
\(^12\) [https://www.medicijnkosten.nl/databankzoekterm=ESCITALOPRAM&toedieningsvorm=TABLETEN%20EN%20CAPSULES](https://www.medicijnkosten.nl/databankzoekterm=ESCITALOPRAM&toedieningsvorm=TABLETEN%20EN%20CAPSULES)
\(^13\) [https://www.legemiddelsok.no/sider/default.aspx?searchquery=escitalopram&f=Han;Mt;Vir;ATC;Var;Mar;Mid;Av;r;gen;par;&pane=0#](https://www.legemiddelsok.no/sider/default.aspx?searchquery=escitalopram&f=Han;Mt;Vir;ATC;Var;Mar;Mid;Av;r;gen;par;&pane=0#)
\(^15\) [https://www.tlv.se/beslut/sok-i-databasen.html?product=escitalopram&tab=1](https://www.tlv.se/beslut/sok-i-databasen.html?product=escitalopram&tab=1)
The following data was made available through personal communications:
Missionpharma (French company, suppliers to Africa): provided the following list of several prices available in India as well as two from the UK.

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<th>Product Name</th>
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* INR/USD and GBP/USD exchange rates as on 23/10/2018
Durbin PLC (UK): a 28-tablet pack of 10 mg escitalopram is available for £2.50, corresponding to $3.28, or $0.12 per pill.

IMRES (Netherlands): Escitalopram is currently sourced from the EU registered generic company Sandoz at USD $1.45 for a pack of 28 tablets, corresponding to $0.05 per pill.

**11.2 Cost-effectiveness**

A search of the Cochrane database for the keyword “escitalopram” yielded 15 Cochrane reviews. Of these, 7 were excluded for irrelevance to depression, and the remaining 8 were excluded for irrelevance to cost-effectiveness.

A search of PubMed for the keywords “escitalopram” and “cost effectiveness” yielded 84 results. Of these, 38 publications were selected for relevance of escitalopram for the treatment of depression that reported cost data by drug administered. On closer review, 8 were excluded for: small sample size (1), poor methodology (1), cost data was obtained by parity from another drug (escitalopram was not marketed in the country at the time of study) (2), review of studies that were already included in more recent reviews included here (1), and duplicates (3). A search of the Cochrane Database of Systematic Reviews yielded no additional studies.

The following reflects the findings from a total of 30 publications. Of those 30, seven were reviewed in one or more of the cited reviews below. These were separately reviewed, and as the authors here largely agree with the findings presented in the review articles, are not additionally reviewed in this text.

**Review articles**

Of the remaining 23 publications, three were review articles. The largest review, published in 2005, included 12 studies, from Sweden, Finland, Norway, Germany, Austria, Netherlands, Belgium, the UK, and the US (1). Eleven of these studies were modeling analyses while one was a prospective multinational analysis, which included data from UK, Germany, France, Spain, Denmark, and Finland (2). The modelling studies consistently demonstrated both direct (healthcare payer) and indirect (societal) cost-effectiveness of escitalopram over generic citalopram, generic or branded fluoxetine, paroxetine, sertraline, and branded venlafaxine, with greater efficacy, measured as remission over a 6-month treatment horizon (1). Sensitivity analyses in these studies comparing escitalopram to fluoxetine, citalopram, paroxetine, and venlafaxine demonstrated the robustness of the models, except for some sensitivity found when the assumed remission rate for escitalopram was varied. The one prospective study the review discussed found the difference in mean total healthcare costs over an eight-week period between escitalopram and venlafaxine XR to be not significantly different (€110 vs. €161) (2). The mean total cost from a societal perspective, both direct and indirect costs, were €765 for escitalopram compared to €873 for venlafaxine XR.

Another review from 2007 (3) which aimed to look at cost-effectiveness of escitalopram compared to citalopram, included seven studies from Finland, Norway, Austria, Belgium, and the UK which all were reviewed in the first review discussed (1) except one study from Finland (4). This review demonstrated lower direct costs (including costs of drugs, suicide, primary and secondary care costs, ranging from approximately €35 to €504) and indirect costs (absenteeism,
ranging from approximately €25 to €1536) per successfully treated patient taking escitalopram compared to those taking citalopram (3).

The third review from 2012, included 8 publications (3 prospective studies, including one (2) from the Murdoch, et al. review (1) and 5 database analyses) with economic evaluations of escitalopram compared to other antidepressants or placebo from the UK, USA, France, and “multisite” (namely several European countries and some data from Canada) (5). The review concluded that patients on escitalopram had lower total healthcare costs than venlafaxine, duloxetine, and other SSRIs, and moreover, that escitalopram appeared more effective than certain SSRIs and duloxetine with respect to treatment persistence, number of hospitalizations, and some clinical symptom measures such as the Sheehan Disability Scale (SDS) and the Montgomery-Asberg Depression Rating Scales-Self reported (MADRS-S). Compared to venlafaxine, patients prescribed escitalopram in some of the included studies showed similar therapeutic effectiveness but at a lower total healthcare cost (5). Of note, all three of the reviews and all but one (6), which did not disclose funding sources, of the included studies in the reviews disclosed conflicts of interest with Lundbeck and other pharmaceutical companies.

**Database analyses**

Three of the 22 included articles were database analyses. One U.S. study compared escitalopram (n=10465) to citalopram (n=4212) over 6-month periods between 2003 and 2005 from the insurer’s perspective and found that the total healthcare costs from multivariate analyses were an average of $1174 less in the escitalopram group (p<.001), and that the average total medical services costs ($972) and total prescription drug costs ($170) were both significantly lower in the escitalopram group (both P <.001) (7). The major depressive disorder (MDD)-related costs (medical service and pharmacy costs related to a diagnosis of MDD) were on average $117 less (P<0.001) per patient in the escitalopram group compared to citalopram. The authors distinguished between the two on the grounds that MDD is often associated with multiple co-morbidities, and that the presence of MDD may in fact worsen outcomes related to those co-morbidities.

A Spanish study of 965 individuals followed for an 18-month period between 2003 and 2007 compared total (direct and indirect) cost-effectiveness of escitalopram to citalopram and venlafaxine (8). In their uncorrected model (in which significant differences in remission rates, age, sex, and various co-morbidities were not corrected for), total costs per patient per year were significantly lower for escitalopram users (€2621.4) compared to citalopram (€3112.3) and venlafaxine (€3715.5) with p values <0.05. When the model was adjusted for the aforementioned differences, the results held: escitalopram users (€2276.20) as compared to citalopram (€3093.80) and venlafaxine (€3801.20) with p values of 0.05. There was additionally a significantly higher rate of remission in those on escitalopram (58%) compared to citalopram (38.3%) at P=<0.001 but not significantly different from the venlafaxine group (32.4%). The summary of these results implies dominance of escitalopram over citalopram and similar cost-effectiveness compared to venlafaxine.

The final database analysis had a different outcome of paroxetine cost-effectiveness, pre and post generic paroxetine introduction into the market, to fluoxetine, sertraline, citalopram, and escitalopram. It too was a 6-month study of patients on these medications between 2001-2004.
The results relevant to escitalopram found that generic but not brand paroxetine dominated escitalopram on direct cost-effectiveness (9). This study declared no conflicts of interest whereas the other two received funding from pharmaceutical companies (Forest Laboratories and Lundbeck).

Modeling analyses
The remaining seventeen publications were modelling studies with a decision-analytic approach, largely from Europe (10–20) and the United States (21–23) but two from Singapore (24,25) and one from Thailand (26). Study periods ranged from as short as 10 weeks (12) to as long as 2 years (19), though the vast majority were 6 months or 1 year. Most studies aimed to compare cost-effectiveness of escitalopram to venlafaxine, duloxetine, and other SSRIs, though one study compared agomelatine to escitalopram and other drugs (19). The primary outcomes of the studies were 1) the effectiveness of the medication, generally measured as remission or meaningful symptom reduction (usually by half) per symptom scales such as the MADRS or the Hamilton Depression Rating Scale (HAM-D) and 2) the expected costs incurred, both from the direct and indirect perspectives. All articles that studied escitalopram against other drugs assumed escitalopram as the first-line treatment, except two (14,23), which looked at cost-effectiveness of escitalopram as a second-line treatment. There was some heterogeneity to the steps used in the decision models, such as variability in the number of lines of treatment (with a maximum of 4th-line treatment) and which medications were designated to each line. An overarching limitation to the results is that all of the studies declared funding sources from or conflict of interests with pharmaceutical companies that market the drug of study. Other limitations were generally addressed by authors, the most concerning of which was populating the model with limited comparative data between medications.

i. Escitalopram vs. venlafaxine
The results of studies comparing escitalopram and venlafaxine were mixed. One study in Belgium showed that while escitalopram dominated, meaning that efficacy achieved was higher at a lower cost, venlafaxine from the societal perspective, it did not dominate from the insurer’s perspective. The calculated incremental cost-effectiveness ratio (ICER) was €6352 per quality-adjusted life year (QALY) (10). At a willingness-to-pay (WTP) threshold of = €30000, there was a 61% probability that escitalopram is the optimal strategy over venlafaxine. A study of nine regions within Italy (18) as well as Sardinia (16) found that escitalopram dominated venlafaxine, but lost dominance when the remission rate of escitalopram was lowered by 5% (18). A Swedish study found that escitalopram dominated venlafaxine from the insurer’s perspective but calculated an ICER of €3732 per QALY from the societal perspective (20). All of these studies modeled costs over a year-long period and did not adjust cost utilities for adverse events. A Dutch study modeled costs over 26 weeks and modulated cost utilities to include medication-related adverse events, finding a direct ICER of €16636 per QALY against venlafaxine but domination with respect to indirect costs (11). With a 5% reduction in escitalopram remission rates, the ICER rose to €39250. In Sweden, over a similar 6-month period and adjusting cost utilities for adverse events, results were that €169.15 would be saved per patient treated with escitalopram over venlafaxine (13). Sensitivity analyses demonstrated a 62.2% probability that escitalopram would be the dominant treatment of 10,000 Monte Carlo patients. At a WTP of €22080, this rose to 78.4% chance, and higher to 82.3% at a WTP of €33600. Meanwhile a Danish study found that cost-effectiveness was similar between escitalopram and venlafaxine.
(15). A Markov-analysis in Germany found similar results, calculating an ICER of €7446 in primary care practices and €9836 in specialist care per successfully treated patient (12). Venlafaxine costs per responder was found to be 34% and 42% higher than escitalopram costs per responder in primary care and specialist care practices respectively. A Swedish study further looked at using escitalopram as a second-line treatment and found it dominated both venlafaxine and duloxetine from the indirect and direct cost perspectives (14). In the U.S., a study of second-line treatments found that the ratio of cost per patient achieve remission for escitalopram was $16,100, second to venlafaxine at $14,275 (23). Moving to Asia, a study in Singapore determined a 68.1% treatment success rate for escitalopram at $2845 per patient as compared to a lower (66%) success rate for venlafaxine at a higher cost of $3176 per patient (25). However, another Singaporean study did not find that escitalopram clearly dominated any drug except duloxetine and in fact was dominated by venlafaxine (24). The Thai study demonstrated that 1768 baht would be saved per patient treated with escitalopram over venlafaxine over the six-month period (26). Overall, the cost-effectiveness of escitalopram as compared to venlafaxine is likely quite similar, given the number of studies that did not find clear dominance between the two, and variable robustness of modeling that did.

**ii. Escitalopram vs. duloxetine**

In the one U.S. study comparing escitalopram to duloxetine, the Markov utility analysis demonstrated clear dominance over duloxetine with a mean one-year direct cost of $903 with a mean estimate efficacy of 41.0 quality-adjusted life weeks (QALW) for escitalopram as compared to $1633 and 38.2 QALWs for duloxetine with no overlap in 95% confidence intervals on either parameter (22). None of the 1000 simulations as part of sensitivity analyses changed the model such that duloxetine was preferred. Nordstrom et al., and Khoo et al., out of Sweden and Singapore respectively also found that escitalopram dominated duloxetine from both the healthcare and societal perspectives (14,24).

**iii. Escitalopram vs. other SSRIs**

Comparisons between escitalopram and other SSRIs were somewhat more robust. In nine regions of Italy (94) as well as Sardinia (95) in Italy, escitalopram dominated venlafaxine XR, sertraline, paroxetine, citalopram, fluoxetine, duloxetine, and fluvoxamine except in Sardinia where the ICER against sertraline was found to be €2120.5 per QALY from the healthcare perspective. On closer look in Lombardy (96), though it was included in the study encompassing nine Italian regions (94), escitalopram dominated citalopram but had an ICER of €1080.0 against paroxetine and €4395.0 against sertraline. The Dutch study found escitalopram dominated citalopram from a societal perspective but calculated an ICER of €7553 per QALY from the healthcare perspective (97). In Denmark, escitalopram dominated citalopram from both perspectives; the total expected cost per successfully treated patient was lower for escitalopram (DKK 22,323 healthcare perspective, DKK 72,399 societal perspective) than for citalopram (DKK 25,778 healthcare perspective, DKK 87,786 societal perspective) (98). The UK’s NICE guideline conducted its own pharmacoeconomic modeling study based on the results of Cipriani et al. 2009 (25) and drug pricing data in the UK in 2008 and concluded that mirtazapine appears to be the dominant option followed by escitalopram or sertraline. The ICERs of escitalopram compared to sertraline were calculated to be £32,987 and £27,172 per QALY for moderate and severe depression respectively, both of which are above the current cost-effectiveness threshold, £20,000 per QALY (4). The final recommendation from the perspective of pharmacoeconomics
for escitalopram was third to mirtazapine and sertraline. A U.S. study found dominance over sertraline with 88.5% probability that escitalopram dominates in 10,000 Monte Carlo simulations (99). Looking at escitalopram as a second-line treatment, its cost-effectiveness ratio at $16,100 topped sertraline at $16,132, generic SSRIs at $16,714, and paroxetine CR at $18,121 per patient achieving remission (100). The study then compared these brand medications to generic SSRIs (fluoxetine, paroxetine, and citalopram), as that is what is usually used as second line treatment, finding that the lowest ICER was $2073 for venlafaxine followed by escitalopram at $3566. In Singapore, a 64.7% treatment success rate for escitalopram at $3133 per patient compared favorably to 60% treatment success rate fluvoxamine at $3297 per patient (101). Savings of 2002 baht per patient treated with escitalopram instead of fluoxetine were found in a Thai modeling study, though one major limitation with this study was that the remission rates in the model were populated with data from head-to-head comparisons between escitalopram and citalopram, as few publications existed at the time comparing escitalopram and fluoxetine (102). A Singaporean decision-analysis over six months found that escitalopram dominated duloxetine and was dominated by venlafaxine and mirtazapine but comparable to several other drugs including fluoxetine, fluvoxamine, paroxetine, sertraline, trazodone, and agomelatine (103). This study represents the least favorable cost-effectiveness profile of all studies here.

**iv Agomelatine vs. escitalopram**

Finally, one study from Greece was included that aimed to measure the cost-effectiveness of agomelatine against SNRIs and SSRIs including escitalopram and generic escitalopram (19). In terms of direct costs, the calculated ICER was €10591 per QALY against escitalopram and €15799 against generic escitalopram. When both indirect and direct costs were taken into consideration, agomelatine dominated escitalopram and the calculated ICER was €3303 for generic escitalopram. Generic escitalopram dominated all other SNRIs and SSRIs in the study from the total cost perspective.

**SUMMARY**

There are several studies from highly developed countries that suggest that escitalopram, as compared to other antidepressants, is a more cost-effective treatment for depression, or at the very least, cost-equivalent, given how few studies found cost-superiority of other medications over escitalopram. Moreover, the UK’s NICE guidelines support the assertion that escitalopram “is better in terms of costs and benefits compared with some of the antidepressants,” and found escitalopram or sertraline to be second choice to mirtazapine from a cost-effectiveness perspective (4). The biggest limitation to the above data is that the vast majority of articles was supported by pharmaceutical companies that manufacture escitalopram. This was somewhat compensated for by sensitivity analyses, assuming the worst possible profile for escitalopram, which still demonstrated some degree of superiority over other available agents. Given that the patent on branded escitalopram in the U.S. expired in 2012, after many of these studies were conducted, one would expect an even more favorable cost-effectiveness profile given current availability of generic versions.
12. Regulatory status

Branded escitalopram was approved by the FDA in 2002 and became generic in 2012. It is approved for acute and maintenance treatment of major depressive disorder in adults and adolescents aged 12-17 and generalized anxiety disorder in adults only (1).

Escitalopram is a nationally authorized medicinal product in several member countries of the European Medicines Agency (EMA) (2) as well as in Canada (3). Escitalopram was first included in the Australian Register of Therapeutic Goods in 2003 and is currently listed for the treatment of major depression, social anxiety disorder, generalized anxiety disorder, and obsessive-compulsive disorder (4). It was approved in Japan in 2011 for the treatment of depression (5). A revision of precautions was made in 2012 stating that patients with prolonged QT was associated with administration of escitalopram (6).

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   https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021323s047lbl.pdf
   Last accessed: 11/5/18
2. European Medicines Agency
   Last accessed: 11/5/18
3. Health Canada
   Last accessed: 11/5/18
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British Pharmacopoeia: No
European Pharmacopoeia: Yes
Indian Pharmacopoeia: Yes
International Pharmacopoeia: No
United States Pharmacopoeia: Yes

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APPENDIX

Letters of Support
Oct 8, 2018

The Secretary of Expert Committee on the Selection and Use of Essential Medicines Medicine Access and Rational Use (MAR) Department of Essential Medicines and Health Products (EMP)
World Health Organization 20 Avenue Appia CH-1211
Geneva 27 Switzerland

Dear Secretariat,

I am writing to you on behalf of the National Center for Mental Health in Korea and I would like to support the application being made by Dr. Iona Kiran Machado at the Stanford University to have escitalopram added to the WHO List of Essential Medicines (WHO EML).

Currently, WHO essential medicines include only amitriptyline and fluoxetine for depressive disorders. The tricyclic antidepressants (TCAs) such as amitriptyline are less well-tolerated than many newer antidepressants including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Fluoxetine is the only SSRI listed in WHO essential medicines. However, differences in individual pharmacology, efficacy, and safety profiles among SSRIs should be taken into consideration to use an appropriate agent for a given patient.

Escitalopram, the active S-enantiomer of racemic citalopram, has been widely used in the treatment of patients with major depression and appears to give superior efficacy and tolerability from a clinical point of view with our many years of experience in medical practice.

The efficacy and safety of escitalopram have been demonstrated by many studies. Escitalopram was significantly more efficacious as well as better tolerated than fluoxetine in meta-analysis conducted on new-generation antidepressants for the acute treatment of major depression in adults [1].

Furthermore, escitalopram was the best cost-effective treatment for depression when compared with many other SSRIs and SNRIs. The expected cost of treatment from escitalopram was cheaper and was associated with a larger health gain in terms of quality adjusted life years (QALYs) than that from fluoxetine [2, 3].

We believe that more than one SSRI should be considered as essential drugs. It is an important point that patients may respond to specific SSRIs differently and it is difficult to predict which agent will be the most effective for each patient. Therefore, I would like to make a special appeal that escitalopram should be added to WHO essential medicines.

Respectfully,

Tae-Yeon Hwang MD, PhD, MPH
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President, Korean Association of Social and Community Psychiatry

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