CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.7443453

Available online at: http://www.iajps.com *Research Article*

FACTS ABOUT OFF-LABEL CLINICAL USES OF ESCITALOPRAM

Fahad S. Alharthi[1], Muslah A. Alanazi[1], Sultan J. Alotaibi[1], Salah A. Alrashid[1], Yousof M. Almutairi[1], Ahmad M AlAyed[1], Ahmad A. Althabaiti[1], Abdullrahman N. Abudalli[2], Shaddi R. Alshammari[3], Abduallh M. Almutairi[3], Amjad A. Almotawa[2,4], Hassan S. alagedi[5], Yousef T. Almutairi[3], Awad M. Alsahfi[6]

[1]Supply Chain Operation Center, Ministry of Health, Riyadh, Saudi Arabia.
[2]General Directorate of Supply Efficiency and General Directorate of Medical Supply, Ministry of Health, Riyadh, Saudi Arabia.
[3]Formulary and Specification Department, Ministry of Health, Riyadh, Saudi Arabia
[4]Wasfaty Department in Assistant Agency for Supply, Ministry of Health, Riyadh, Saudi Arabia.
[5]Pharmaceutical Planning Department, Ministry of Health, Riyadh, Saudi Arabia.
[6]Khulais General Hospital, Makkah Health Cluster, Ministry of Health, Makkah, Saudi Arabia.

Article Received: November 2022 **Accepted:** November 2022 **Published:** December 2022

Abstract:

Escitalopram is a drug originally approved treatment of major depressive disorders (MDD). In the pharmacotherapy of obsessive compulsive disorders (OCD), general anxiety disorder (GAD) and post-traumatic stress disorder (PSTD), escitalopram may be considered a first-line treatment due to its good tolerability and lack of withdrawal symptoms. However, aside approved uses of escitalopram, the drug has found clinically-evidence-based uses for which it was not originally recognized. The objective of this review was to evaluate the unapproved uses of escitalopram in medicine. Electronic searches for relevant literature were undertaken in Google scholar, MEDLINE, EMBASE, PubMed, and Science Direct. Literatures and studies were considered in which escitalopram uses, facts about clinical uses of escitalopram, off-label uses, and limitations of the off-label uses were discussed. Eating disorders, pain management, premature ejaculation, autism spectrum disorders, cancer, hot flashes and premenstrual syndrome were identified as some of the off-label uses of escitalopram. For eating disorders; major depressive disorder, anxiety disorder, and obsessive compulsive disorder associated with abnormal eating patterns are all serious mental illnesses that often occur together, therefore escitalopram is used to alleviate the symptoms and conditions such as obesity resulting from this disorders. Escitalopram may alleviate pain through a number of different processes. Neuropathy pain can be alleviated by antidepressants because of their ability to block sodium channels. Patients with persistent erectile dysfunction (PE) whose condition is managed with daily escitalopram medication have reportedly seen changes in semen parameters. Some studies mentioned that escitalopram use gave relief from hot flashes and other menopausal symptoms within one week. Hepatocellular carcinoma (HCC) and autism were identified as other diseases managed with escitalopram. Lack of sufficient data to support use, and proliferated chances for adverse events were included as the drawbacks of off-label uses of escitalopram. However, certain factors such as fewer availability of approved treatments for the illness are considered in the off-label uses of escitalopram. Although escitalopram expands therapy possibilities for some individuals who had none before, it's crucial to remember that it does have some adverse effects that may lessen the quality of life for those who take it. Depression is a comorbidity for many of the off-label disorders. Therefore, in many circumstances, the antidepressant may just alleviate symptoms while more therapy is required to address the underlying cause of the depression. Evidence on off-label antidepressant usage must be generated and provided to clinicians in order to improve prescribing practices.

Corresponding author:
Fahad S. Alharthi,
Supply Chain Operation Center, Ministry of Health, Riyadh, Saudi Arabia.

QR code

Please cite this article in press Fahad S. Alharthi et al, ***Facts About Off-Label Clinical Uses Of Escitalopram..,*** *Indo Am. J. P. Sci, 2022; 09(12).*

BACKGROUND:
One hundred European, North American, and other countries authirused the use of escitalopram over a decade ago(1). Escitalopram (Cipralex®, Lexapro®) is an SSRI that has been proven effective in the treatment of MDD and anxiety disorder(1). In furthermore, escitalopram has been found to have a protective effect on the relapse and recurrence of MDD when administered over the long term. Escitalopram is recommended for the treatment of major depressive disorder (MDD), obsessive-compulsive disorder (OCD), panic disorder (panic attack), social anxiety disorder (SAD), and generalized anxiety disorder (GAD) (1). Patients with social anxiety disorder (SAD) treated with any dose of escitalopram showed statistically and clinically significant improvement compared to those treated with placebo (2). There is promising evidence that the benefit-risk ratio for escitalopram in SAD is favorable, given the drug's efficacy and its acceptable safety.

In the pharmacotherapy of OCD, GAD, PTSD, and social phobia, it may be considered a first-line treatment due to its good tolerability and lack of withdrawal symptoms (3).

Of all SSRIs, it has the greatest therapeutic window. It is a type of medication known as a selective serotonin reuptake inhibitor (4). The serotonin transporter in humans is inhibited in a dose- and selectivity-dependent manner by this medication (1). It increases serotonin activity in the brain by blocking its reabsorption at presynaptic nerve terminals. Allosteric action is present in escitalopram as well. It also has a low potential for medication interactions (1). (3).
It is the S-enantiomer of citalopram 2, making it a racemic citalopram (RS-citalopram) that contains both the active S-enantiomer and the clinically ineffective R-enantiomer (1,5). The S-enantiomer of RS-citalopram, which is the active form, was isolated to create escitalopram.

METHODS:
Electronic searches for relevant literatures were undertaken in Google scholar, MEDLINE, EMBASE, PubMed, and Science Direct. The keywords queries used were ‘off-label uses of escitalopram’, ‘escitalopram’, uses of ‘escitalopram’, ‘unapproved uses of escitalopram’. 197 relevant published studies and literatures were listed by the searches, 63 of them were identified as relevant and evaluated for key information. 48 of the Literatures and studies were considered and referenced in which escitalopram uses, facts about clinical uses of escitalopram, off-label uses, and limitations of the off-label uses were discussed.

RESULTS:
Off-label uses (Uses not approved by the FDA)
Repurposing the medicine is one example of off-label use. Another definition of "off-label" is when a drug is used in a way that deviates from the norm, whether it be through dosing, duration, frequency, route of administration (e.g., orally as opposed to intravenously), or patient population (e.g. children instead of adults). A medicine cannot be marketed by a pharmaceutical company for a use that has not been authorized by a regulatory body like the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) (EMA). While it is against the law to promote a drug for an unapproved use, it is not against the law for a doctor to prescribe a drug for an unapproved use. (6). Premenstrual dysphoric disorder, hot flashes sensations of menopause, and pain management are some of the conditions for which escitalopram is used off-label (4).

Eating Disorders (ED)
Aberrant eating habits are diagnostic of an eating disorder and have deleterious effects on a person's nutritional intake and overall well-being. Anorexia nervosa, bulimia nervosa, and binge eating disorder are the three most common types of eating disorders (6). Major depressive disorder, anxiety disorder, and

obsessive-compulsive disorder are all serious mental illnesses that often occur together (7,8). Significantly low body weight, an extreme fear of weight increase, and a distorted body perception are the major criteria for making a diagnosis of anorexia nervosa (6). Recurrent binges (overeating linked with lack of control) and improper coping behavior, including vomiting, extreme activity level, or skipping meals, are diagnostic criteria for bulimia nervosa. The most frequent form of eating disorder is binge eating disorder, which differs from bulimia nervosa in that those affected do not engage in excessive compensatory behaviors after bingeing. Underdiagnosed and inadequately treated, an eating problem is strongly linked to obesity (7). Improvements in therapy are needed since eating disorders have the greatest mortality rate of any mental health disease (9). While high-dose escitalopram has been shown to be effective in reducing both weight and the overall severity of illness, it may not be effective in reducing the obsessive-compulsive symptoms of BED (10).

The FDA-approved prescription for binge eating disorder is lisdexamfetamine, a prodrug of D-amphetamine, and it is generally recommended above antidepressants. However, antidepressants may be warranted as first-line treatment for those who also suffer from co-occurring conditions including anxiety and depression. Treatment of bulimia nervosa with a single antidepressant has been shown to be beneficial in clinical trials, however this cannot be said for anorexia nervosa (8). Escitalopram and other antidepressants should be taken in conjunction with dietary rehabilitation and talk therapy (8). The involvement of the serotonin, noradrenaline, and dopamine systems in the pathophysiology of bulimia nervosa and binge eating disorder may account for the success of antidepressants in treating these conditions (11,12).

As of yet, there is no treatment for AN that has been approved by the Food and Drug Administration in the United States, and those that do exist are not particularly effective (8). Because of their limited effectiveness (8), antidepressants are not recommended as a stand-alone therapy for anorexia, and instead should be used in conjunction with dietary rehabilitation and psychotherapy. When it comes to the acute treatment phase of anorexia in underweight individuals, there is a general lack of evidence to support the use of SSRIs. Clinicians should therefore avoid giving antidepressants to patients while they are in the hospital working to regain their weight and nutrition. Once a person's weight has been recovered, the next step in treatment is maintenance, but at this time there is conflicting evidence about the role of SSRIs and the benefits they provide for those with anorexia. When prescribing an SSRI, doctors need to utilize their best judgment. Anorexic individuals who have had their weight restored may have a higher chance of long-term success with treatment if they undergo a mix of psychotherapy and various pharmaceutical modalities, with the premise that their efficacy may be additive or even synergistic.

Night eating syndrom (NES) is a rare condition in which a person experiences extreme hunger just before bedtime or in the middle of the night. Treatment with escitalopram for 12 weeks was not more effective than placebo in decreasing NES symptoms in a randomized controlled trial (13). Anorexia has a built-in resistance to treatment (14). Medication and CBT used together have been more successful than either method alone in treating BN and BED. Unfortunately, there is a lack of information regarding the long-term effectiveness of pharmacotherapy for EDs. Pharmacotherapy for EDs, both short and long term, continues to present difficulties for clinicians. (14).

Managing episodes of binge eating and reducing excess weight are common treatment objectives for those who suffer from binge eating disorder (15). Dietary and lifestyle changes, talk therapy, and pharmaceuticals are only some of the treatments that have been tried. The binge eating behavior can be reduced with diet and lifestyle modifications, and one can expect to lose some weight as a result. Numerous psychotherapies have been useful, most notably in halting binge eating, although these programs often have a negligible effect on reducing body mass. Several pharmaceutical therapies have been created, with an emphasis on antidepressants (used for their anti-binge eating effects) and weight loss medications. Both have been demonstrated to have some degree of usefulness, though, as before, antidepressants appear to have a particularly hard time resulting in sustained weight loss. Psychotherapy in conjunction with pharmaceutical treatment, if available, is likely the most effective method for treating binge eating disorder.

Chronic Pain management

Rheumatoid arthritis (RA) is a chronic inflammatory disorder for which there is presently no cure, and chronic pain is a common symptom. As a result, the primary goals of RA treatment are pain reduction and functional enhancement. Similarly to other chronic pain diseases, antidepressants are used to treat RA. Even though there are a number of studies that

compare antidepressant medication to other treatments for RA (such as placebo and non-pharmacological therapies), these trials are not strong enough to draw any conclusions about the efficacy of the antidepressants (16). One case report describes a patient with rheumatoid arthritis (RA) whose symptoms improved while using escitalopram (an SSRI) for depression (17). To completely justify the prescription of antidepressants for patients with RA, more high-quality clinical trials are needed in this sector. We still don't understand the underlying mechanisms through which antidepressants relieve pain. Simplest of all, these medications work by raising levels of neurotransmitters in the spinal cord, which in turn dampens pain signals. However, antidepressants are notoriously sluggish in their effects.

Antidepressants may alleviate pain through a number of different processes. Neuropathy pain can be alleviated by antidepressants because of their ability to block sodium channels (18). This results in an inhibition of discharges from damaged nerves (19).

Despite the absence of a depressive episode in certain patients, antidepressants are frequently used for the management of chronic pain in a variety of settings. Unfortunately, the antidepressant doses used in such medical procedures are typically lower than what is necessary to exhibit antidepressant effects.

Premature Ejaculation

Most PE medications are either experimental or are used off-label, hence there is no definitive treatment for PE. (20). Selective serotonin reuptake inhibitors have emerged as the primary and first-line treatment for lifelong premature ejaculation (PE) thanks to the neurobiological approach (21). Prompt ejaculation can be effectively treated with selective serotonin reuptake inhibitors (SSRIs) like escitalopram (22). Antidepressants for premature ejaculation have been studied, and escitalopram, being one of the most well-known selective serotonin reuptake inhibitors, was utilized in this research. Intravaginal ejaculatory latency time (IELT) showed a delay in ejaculation after daily escitalopram 10 mg treatment for patients with definite PE. Furthermore, any drug-related adverse effects that did surface during treatment generally diminished and became minimal by the fourth week. (16).

In contrast, escitalopram treatment was associated with statistically and clinically significant decreases in sperm concentration, motility, and morphology relative to pre-treatment levels (23). Patients with persistent erectile dysfunction (PE) whose condition is managed with daily escitalopram medication report changes in semen parameters. It is not known why SSRIs differ in their inhibitory action on ejaculation, despite the fact that they are all active in the same diseases, such as depression, anxiety disorders, obsessive-compulsive disorder, and others. (22).

Hot flashes

The use of antidepressants to alleviate hot flashes experienced by menopausal women is supported by substantial evidence. Escitalopram is an example of such antidepressants (24). Another study indicated that Escitalopram at doses of 10-20 mg daily is an effective and well-tolerated non-hormonal off-label treatment for menopausal hot flashes in healthy women (25). Relief from hot flashes and other menopausal symptoms is observed to be immediate (within one week), making this a potentially viable and effective therapy option for women in generally good health who might not otherwise seek antidepressant treatment (26),(27).

Autism

Patients with Autism Spectrum Disorder (ASD) are often prescribed selective serotonin reuptake inhibitors like escitalopram (28).

Cancer

There is little hope for patients diagnosed with hepatocellular carcinoma (HCC). There is new evidence that SSRIs like escitalopram can decrease cancer growth (29). As such, the results of this trial provide credence to the idea that escitalopram may have therapeutic value in the treatment of HCC.

The drawbacks of off-label uses.

Antidepressants have been widely recommended by primary care physicians for reasons other than depression over the past decade. And when antidepressants weren't being taken for depression, it was discovered that over half of all prescriptions were being used for something other than what the manufacturer intended (30).

When there is insufficient data to prove that the benefits of the drug outweigh the risks, off-label prescribing must be closely monitored (31,32). Use of ineffective antidepressants is worrisome because it results in wasteful spending and puts patients at risk for unpleasant side effects and perhaps life-threatening adverse events. For instance, newer antidepressants like selective serotonin reuptake inhibitors (SSRIs) are more expensive and have been linked to notable side effects and safety issues than older antidepressants like

tricyclic antidepressants (TCAs), despite being safer and more palatable. Sexual dysfunction, sleepiness, insomnia, weight gain, and fatigue (33-35); increased risk of fractures14 and upper gastrointestinal bleeding; fatigue; drowsiness; insomnia; (36,37). Furthermore, patients who take antidepressants off-label may be at risk for adverse effects if their clinical characteristics differ from those of the patient populations used in the drug's pre-market clinical trials (38). Using a medicine outside of its approved indication increases the chance of adverse events by 54% compared to when the drug is used in accordance with the manufacturer's instructions (39).

Estimates suggest that 29% of antidepressants are used for purposes other than those approved by the FDA(40), although it is not known how often or to what extent this occurs. As a result, Wong et al. conducted research into the credibility of antidepressants' unapproved usage. Scientific support for using escitalopram for off-label purposes in the treatment of panic disorders was established by the study.

Considerations for Unapproved Uses

Doctors may prescribe antidepressants for unapproved uses due to a number of factors in the patient's environment. As the number of drugs available to doctors continues to grow, it becomes increasingly difficult for them to keep track of which patients can safely take which medications,(41) especially considering that some drug corporations have been caught promoting their products for unapproved uses (42). Pharmaceuticals of the same class may be assumed to be interchangeable by doctors, therefore external factors like health insurance formularies may affect which drugs doctors choose to prescribe (43,44). Patients participating in the public drug insurance plan, for instance, may not have access to escitalopram in some healthcare facilities. Patients covered by public medication insurance may only get escitalopram 4.7% of the time, but citalopram 51.4% of the time from the study physicians who prescribe SSRIs. Study doctors may prescribe either escitalopram or citalopram to patients covered by private drug plans (29.3% and 31.7% of all SSRI prescriptions for patients with private drug plans, respectively) (30).

Third, if other therapies for a given indication are contraindicated or seen as greater risk drugs, primary care providers might prescribe antidepressants off-label. As an illustration, benzodiazepines and Z medicines like zolpidem and zaleplon have shown successful in treating insomnia (45). These medications, however, have been labeled as possibly inappropriate therapies for older persons and, if prescribed, could even have a detrimental impact on providers' quality and performance metrics (46). As a result, many doctors may opt to utilize trazodone as an alternative medication for their elderly patients since they consider it to be less dangerous.

These results highlight the need of taking into account the quality of evidence supporting risk-benefit when prescribing an antidepressant, particularly if the medicine is known to have significant unpleasant side effects. In the absence of conclusive data, doctors should proceed with care, prescribe conservatively, and involve patients in the decision-making process (47).

Even though manufacturers are prohibited from promoting "off-label" usage, there is a possibility that such uses are beneficial medical procedures (48). Neither on-label nor off-label use of drugs are restricted by the FDA. If a drug's maker determines that the effort required to add new indications to the drug's label is worthwhile, a supplemental new drug application can be filed (43). A pharmaceutical company must spend resources gathering data and going through the FDA filing process in order to obtain a designated indication. If the drug in question has gone generic, it's possible that investing in the company would be a waste of money. Because of this, the label may not accurately reflect the state of knowledge regarding the efficacy of the drug.

Off-label uses of antidepressants are commonly symptom-based diseases for which there are no FDA-approved medication therapies. A lack of appropriate pharmacotherapy may be reflected in the fact that primary care physicians are turning to antidepressants as a treatment of last resort for certain disorders.

Understanding the contexts in which there may be a disincentive to seek a change in a designated indication, even when essential, can be gained by studying how drugs are administered off label. Additionally, it may highlight areas where additional physician education is required, such as when a certain off-label use has been found to be hazardous or ineffective yet the medication is still being administered. Finally, by looking at off-label use, opportunities can be found to conduct more rigorous studies to corroborate the perceived effectiveness in clinical practice.

CONCLUSION:

In recent years, there has been a dramatic increase in the use of antidepressants like escitalopram in Western countries. This is partly because of all the ways people are putting them to use that aren't technically approved by the FDA. Although escitalopram expands therapy possibilities for some individuals who had none before, it's crucial to remember that it does have some adverse effects that may lessen the quality of life for those who take it. Depression is a comorbidity for many of the off-label disorders. Therefore, in many circumstances, the antidepressant may just alleviate symptoms while more therapy is required to address the underlying cause of the depression.

Evidence on off-label antidepressant usage must be generated and provided to clinicians in order to improve prescribing practices.

REFERENCES:

1. Kirino E. Escitalopram for the management of major depressive disorder: a review of its efficacy, safety, and patient acceptability. Patient Prefer Adherence. 2012 Dec;853.
2. Baldwin DS, Asakura S, Koyama T, Hayano T, Hagino A, Reines E, et al. Efficacy of escitalopram in the treatment of social anxiety disorder: A meta-analysis versus placebo. Eur Neuropsychopharmacol. 2016 Jun;26(6):1062–9.
3. Bareggi SR, Mundo E, Dell'Osso B, Altamura AC. The use of escitalopram beyond major depression: pharmacological aspects, efficacy and tolerability in anxiety disorders. Expert Opin Drug Metab Toxicol. 2007 Oct;3(5):741–53.
4. Landy K, Rosani A, Estevez R. Escitalopram [Internet]. StatPearls Publishing; 2022 [cited 2022 Jan 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557734/
5. Sánchez C, Bergqvist PBF, Brennum LT, Gupta S, Hogg S, Larsen A, et al. Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent effects in animal models predictive of antidepressant and anxiolytic activities. Psychopharmacology (Berl). 2003 Jun;167(4):353–62.
6. Skånland SS, Cieślar-Pobuda A. Off-label uses of drugs for depression. Eur J Pharmacol. 2019 Dec;865:172732.
7. Amodeo G, Cuomo A, Bolognesi S, Goracci A, Trusso MA, Piccinni A, et al. Pharmacotherapeutic strategies for treating binge eating disorder. Evidence from clinical trials and implications for clinical practice. Expert Opin Pharmacother. 2019 Apr 13;20(6):679–90.
8. Marvanova M, Gramith K. Role of antidepressants in the treatment of adults with anorexia nervosa. Ment Health Clin. 2018 May 1;8(3):127–37.
9. Gibson D, Workman C, Mehler PS. Medical Complications of Anorexia Nervosa and Bulimia Nervosa. Psychiatr Clin North Am. 2019 Jun;42(2):263–74.
10. Guerdjikova AI, McElroy SL, Kotwal R, Welge JA, Nelson E, Lake K, et al. High-dose escitalopram in the treatment of binge-eating disorder with obesity: a placebo-controlled monotherapy trial. Hum Psychopharmacol Clin Exp. 2008 Jan;23(1):1–11.
11. Latagliata EC, Patrono E, Puglisi-Allegra S, Ventura R. Food seeking in spite of harmful consequences is under prefrontal cortical noradrenergic control. BMC Neurosci. 2010 Dec;11(1):15.
12. Monteleone P, Tortorella A, Castaldo E, Maj M. Association of a functional serotonin transporter gene polymorphism with binge eating disorder. Am J Med Genet B Neuropsychiatr Genet. 2006 Jan 5;141B(1):7–9.
13. Vander Wal JS, Gang CH, Griffing GT, Gadde KM. Escitalopram for Treatment of Night Eating Syndrome: A 12-Week, Randomized, Placebo-Controlled Trial. J Clin Psychopharmacol. 2012 Jun;32(3):341–5.
14. Flament MF, Bissada H, Spettigue W. Evidence-based pharmacotherapy of eating disorders. Int J Neuropsychopharmacol. 2012 Mar;15(02):189–207.
15. Crow S. Treatment of Binge Eating Disorder. Curr Treat Options Psychiatry. 2014 Dec;1(4):307–14.
16. Richards BL, Whittle SL, Buchbinder R. Antidepressants for pain management in rheumatoid arthritis. Cochrane Musculoskeletal Group, editor. Cochrane Database Syst Rev [Internet]. 2011 Nov 9 [cited 2022 Dec 1]; Available from: https://doi.wiley.com/10.1002/14651858.CD008920.pub2
17. Krishnadas R, Krishnadas R, Cavanagh J. Sustained remission of rheumatoid arthritis with a specific serotonin reuptake inhibitor antidepressant: a case report and review of the literature. J Med Case Reports. 2011 Mar 19;5:112.
18. Dick IE, Brochu RM, Purohit Y, Kaczorowski GJ, Martin WJ, Priest BT. Sodium Channel Blockade May Contribute to the Analgesic Efficacy of Antidepressants. J Pain. 2007 Apr;8(4):315–24.

19. Zuliani V, Rivara M, Fantini M, Costantino G. Sodium channel blockers for neuropathic pain. Expert Opin Ther Pat. 2010 Jun;20(6):755–79.
20. Saleh R, Majzoub A, Abu El-Hamd M. An update on the treatment of premature ejaculation: A systematic review. Arab J Urol. 2021 Jul 3;19(3):281–302.
21. Zaazaa A, Selim O, Hosny Awad H, Soltan G, Ghanem H. Safety and efficacy of escitalopram in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. Hum Androl. 2012 Mar;2(1):16–8.
22. Arafa M, Shamloul R. A randomized study examining the effect of 3 SSRI on premature ejaculation using a validated questionnaire. Ther Clin Risk Manag. 2007 Aug;3(4):527–31.
23. Koyuncu H, Serefoglu EC, Yencilek E, Atalay H, Akbas NB, Sarıca K. Escitalopram treatment for premature ejaculation has a negative effect on semen parameters. Int J Impot Res. 2011 Nov;23(6):257–61.
24. LaCroix AZ, Freeman EW, Larson J, Carpenter JS, Joffe H, Reed SD, et al. Effects of escitalopram on menopause-specific quality of life and pain in healthy menopausal women with hot flashes: A randomized controlled trial. Maturitas. 2012 Dec;73(4):361–8.
25. Freeman EW. Efficacy of Escitalopram for Hot Flashes in Healthy Menopausal Women: A Randomized Controlled Trial. JAMA. 2011 Jan 19;305(3):267.
26. Defronzo Dobkin R, Menza M, Allen LA, Marin H, Bienfait KL, Tiu J, et al. Escitalopram reduces hot flashes in nondepressed menopausal women: A pilot study. Ann Clin Psychiatry Off J Am Acad Clin Psychiatr. 2009;21(2):70–6.
27. Mori C, Imai A. Relief of hot flashes with escitalopram in non-depressed menopausal women in Japan: Results of a retrospective analysis. Health (N Y). 2012;04(10):893–6.
28. Bishop JR, Najjar F, Rubin LH, Guter SJ, Owley T, Mosconi MW, et al. Escitalopram pharmacogenetics: CYP2C19 relationships with dosing and clinical outcomes in autism spectrum disorder. Pharmacogenet Genomics. 2015 Nov;25(11):548–54.
29. Chen LJ, Hsu TC, Chan HL, Lin CF, Huang JY, Stewart R, et al. Protective Effect of Escitalopram on Hepatocellular Carcinoma by Inducing Autophagy. Int J Mol Sci. 2022 Aug 17;23(16):9247.
30. Wong J, Motulsky A, Abrahamowicz M, Eguale T, Buckeridge DL, Tamblyn R. Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system. BMJ. 2017 Feb 21;j603.
31. Dresser R, Frader J. Off-Label Prescribing: A Call for Heightened Professional and Government Oversight. J Law Med Ethics. 2009;37(3):476–86.
32. O'Malley PG. What does off-label prescribing really mean? Arch Intern Med. 2012 May 28;172(10):759–60.
33. Cascade E, Kalali AH, Kennedy SH. Real-World Data on SSRI Antidepressant Side Effects. Psychiatry Edgmont Pa Townsh. 2009 Feb;6(2):16–8.
34. Hu XH, Bull SA, Hunkeler EM, Ming E, Lee JY, Fireman B, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. J Clin Psychiatry. 2004 Jul;65(7):959–65.
35. Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychother Psychosom. 2016;85(5):270–88.
36. Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2009 Dec;7(12):1314–21.
37. Anglin R, Yuan Y, Moayyedi P, Tse F, Armstrong D, Leontiadis GI. Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis. Am J Gastroenterol. 2014 Jun;109(6):811–9.
38. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. Mayo Clin Proc. 2012 Oct;87(10):982–90.
39. Eguale T, Buckeridge DL, Verma A, Winslade NE, Benedetti A, Hanley JA, et al. Association of Off-label Drug Use and Adverse Drug Events in an Adult Population. JAMA Intern Med. 2016 Jan;176(1):55–63.
40. Wong J, Motulsky A, Eguale T, Buckeridge DL, Abrahamowicz M, Tamblyn R. Treatment Indications for Antidepressants Prescribed in Primary Care in Quebec, Canada, 2006-2015. JAMA. 2016 May 24;315(20):2230.
41. Chen DT, Wynia MK, Moloney RM, Alexander GC. U.S. physician knowledge of the FDA-

approved indications and evidence base for commonly prescribed drugs: results of a national survey. Pharmacoepidemiol Drug Saf. 2009 Nov;18(11):1094–100.
42. Ghinea N, Lipworth W, Kerridge I. x? Ther Innov Regul Sci. 2015 May;49(3):359–63.
43. Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. N Engl J Med. 2008 Apr 3;358(14):1427–9.
44. Sbarbaro JA. Can we influence prescribing patterns? Clin Infect Dis Off Publ Infect Dis Soc Am. 2001 Sep 15;33 Suppl 3:S240-244.
45. Wilson S, Nutt D, Alford C, Argyropoulos S, Baldwin D, Bateson A, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol (Oxf). 2010 Nov;24(11):1577–601.
46. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012 Apr;60(4):616–31.
47. Largent EA, Miller FG, Pearson SD. Going off-label without venturing off-course: evidence and ethical off-label prescribing. Arch Intern Med. 2009 Oct 26;169(19):1745–7.
48. O'Brien PL, Cummings N, Mark TL. Off-Label Prescribing of Psychotropic Medication, 2005–2013: An Examination of Potential Influences. Psychiatr Serv. 2017 Jun;68(6):549–58.