Selective Serotonin Reuptake Inhibitors and Risk of Gastrointesinal Bleeding In Dyspepsia: An Evidence-Based Case Report

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ABSTRACT

Aim: *This evidence-based case report aims to provide the latest evidence about the risk of gastrointesinal (GI) bleeding in selective serotonin reuptake inhibitor (SSRI) users with dyspepsia.*

Method: *The literature search was conducted in four major electronic databases (PubMed, Cochrane, Scopus, ProQuest). The selected articles were sorted through screening abstract based on the inclusion and exclusion criteria. Critical appraisal was performed by using validated critical appraisal tool.*

Results: *Of 247 records from extensive literature searching, three eligible studies (one randomized clinical trial and two cohort studies) were obtained to answer the clinical question. All studies showed SSRIs did not increase the risk of GI bleeding in patients with functional dyspepsia and peptic ulcer. However, the adverse event of SSRIs might be under-reported.*

Conclusion: *According to the evidence, the risk of GI bleeding in SSRIs users with dyspepsia is still unclear. Larger size of sample of controlled trial study is recommended to be conducted to calculate the precise risk of GI bleeding in SSRI users with dyspepsia.*

Keywords: *selective serotonin reuptake inhibitor, GI bleeding, dyspepsia*

ABSTRAK

Tujuan: *Laporan kasus berbasis bukti ini bertujuan untuk mendapatkan bukti terbaru mengenai risiko perdarahan saluran cerna pada pasien dispepsia fungsional maupun organik yang mengonsumsi selective serotonin reuptake inhibitor (SSRI).*

Metode: *Pencarian lieratur dilakukan menggunakan 4 database pencarian utama (PubMed, Cochrane, Scopus, Proquest). Artikel terpilih disortir melalui skrining abstrak berdasarkan krieria inklusi dan eksklusi yang telah ditetapkan. Telaah kritis mengguinakan alat bantu yang telah divalidasi sebelumnya.*

Hasil: *Dari 247 artikel yang diperoleh dari pencarian literatur, 3 artikel (1 studi uji klinis acak dan 2 studi kohort) yang dapat digunakan untuk menjawab pertanyaan klinis. Seluruh studi menunjukkan bahwa SSRIs tidak menunjukkan risiko perdarahan saluran cerna pada pasien dispepsia fungsional dan ~~ulkus peptikum~~ dispepsia organik. Akan tetapi, efek samping SSRIs yang sebenarnya lebih tinggi dari yang dilaporkan.*

Simpulan: *Berdasarkan bukti yang diperoleh, risiko perdarahan saluran cerna pada pasien dispepsia yang menggunakan SSRI masih belum jelas. Diperlukan penelitian uji klinis dengan jumlah sampel yang lebih besar untuk dapat memperkirakan risiko perdarahan saluran pada pasien dispepsia yang menggunakan SSRIs.*

Kata kunci: *selective serotonin reuptake inhibitor, perdarahan saluran cerna, dispepsia*

INTRODUCTION

Dyspepsia is a medical term that encompass all of symptoms originating from the upper gastrointestinal tract, including epigastric pain, epigastric burning, postprandial fullness, and early satiety.[9] One third of patients visit general practitioners with chief complaint of dyspepsia, resulting one of the most cases found in daily clinical practice. In Jakarta, the proportion of dyspepsia was reported as high as 58.1% from 1,645 participants.[10] In general, dyspepsia was classified into organic (ulcer and cancer) and functional dyspepsia. Rome IV classified the functional dyspepsia into two subclassess postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS).[11] Surprisingly, the prevalence of functional dyspepsia was estimated 30–40%. Gastric neuromuscular dysfunction, dysmotilty, low grade inflammation, pyschological distress have been associated with functional dyspepsia.[12] The diagnosis of functional dyspepsia is challenging and needs to exclude the organic etiology. Stomach erosion or gastritis from endoscopic finding do not necessarily explain the symptoms and thus do not contradict a diagnosis of functional dyspepsia.

Psychological factors and emotional distress are identified as important contributors of functional dyspepsia and also organic dyspepsia (peptic ulcer disese). In a study of a small sample of dyspepsia patients, the Depression, Anxiety and Stress scale (DASS) revealed that 82.5% had anxiety, 60% had depression, and 67.5% had stress, while those with more pronounced anxiety symptoms were more likely to have endoscopic inflammatory alterations. The significant co-morbidity between gastrointestinal and psychologic problems and the frequent use of antidepressants to treat GI conditions point to a bidirectional gut-brain network that connects emotional, cognitive, and gut processes. Some patients with dyspepsia have been demonstrated to benefit from antidepressants. Luo et al in 2019 reported that he small dose antidepressant SSRI therapy (citalopram and fluoxetin) was effective for refractory functional dyspepsia. The improvement of symptoms was found in 93.8% patients within 1 year follow-up period.[13]

Anxiety disorders are the most common psychological disorders. which currently have a global prevalence of 7.3% (4.8%-10.9%). In US, anxiety disorders have a lifetime prevalence od approximately 34%. There is not enough data to say whether these illnesses have gotten more common in recent years. In general, women are more likely than men to experience emotional problems that first appear during adolescence; they are 1.5 to 2 times more likely to experience an anxiety disorder than males. Worry, performance and social anxiety, unexpected and/or triggered panic attacks, anticipatory anxiety, and avoidance behaviors are some of the symptoms of anxiety disorders. The most prevalent anxiety disorders seen in primary care are generalized anxiety disorder (6.2% lifetime prevalence), social anxiety disorder (13% lifetime prevalence), and panic disorder (5.2% lifetime prevalence) with or without agoraphobia.

Generalized anxiety disorder (GAD) is charecterized by persistent, excessive, and irrational worry over routine events. This anxiety may have multiple focuses, including money, family, health, and the future. It is excessive, challenging to manage, and frequently accompanied by a wide range of vague psychological and physical symptoms. The hallmark of generalized anxiety disorder is excessive worry. The following are some of the diagnostic standards in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5):

- Excessive anxiety and worry for at least six months
- Difficult controlling the worrying
- The anxiety is associated with three or more of below symptoms for at least 6 months:
    1. Restlessness, feeling keyed up or on edge
    2. Being easily fatigued
    3. Difficulty in concentrating or mind going blank, irritability
    4. Muscle tension
    5. Sleep disturbance
    6. Irritability

- The anxiety results in significant distress or impairment in social and occupational areas.
- The anxiety is not attributable to any physical cause.

Cognitive behavioral therapy and medicines are the two main therapies for generalized anxiety disorder. A combination of the two might be most advantageous for patients. Clinicians should take into account the patient's preferences, previous and ongoing therapies, co-occurring physical and mental conditions, age, sex, and plans for having children, as well as cost and availability to care, when choosing a course of treatment. The bio-psycho-social model for anxiety disorders is the last one to be put forth.

Medication may be used to treat patients who do not respond to cognitive behavioral therapy. Generalized anxiety disorder is treated with a variety of drugs. Selective serotonin reuptake inhibitor (SSRI) is recommended as the first line antidepressant therapy, due to the fewer side effect and more favorable safety profile, and also used in anxiety such as GAD on long term use[4,5] Food and Drug Administration (FDA) US initially approved SSRI only for the treatment of depression. Currently, several conditions could be managed with SSRI including ~~anxiety disorders~~,depression, autism spectrum disorders, eating disorders, premenstrual syndrome, even with gastrointestinal disorders.[6]

As mentioned before, SSRI become the first line-therapy because of generally better tolerated than other antidepressants. However, several common side effects also reported, such as nausea, vomiting, headache, drowsiness, insomnia, reduced libido, and agitation. Extrapyramidal symptoms (EPS), serotonin syndrome, prolonged QT duration, congenital anomalies, skin rash, dan cataracts are also reported to be associated with SSRI consumption.[6] The SSRI was also linked with the increased risk of gastrointestinal (GI) bleeding. Study by Dalton et al in 2003, is one of the earlier study that examine the risk of upper GI bleeding in patients who consumed antidepressant. This population-based cohort during 1991–1995 period found that the incidence of upper GI bleeding increased 3.6 times more than expected with the use of SSRI. Combination of SSRI with non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin was further increased the bleeding risk to 12.2 times.[7]

Anglin et al in 2014 conducted a systematic review and meta-analysis to acquire more precise estimation of risk of upper GI bleeding with SSRI. As many as 15 case-control studies and 4 cohort studies were included in this study. The risk of upper GI bleeding was found increase in case control studies (OR = 1.66; 95% CI: 1.44–1.92) and cohort studies (OR = 1.68; 95% CI: 1.13–2.50). The further increased of upper GI bleeding was found in patients use both NSAID dan SSRI with OR = 4.25; 95% CI 2.82–6.42.[8]

The safety profile of SSRI, particularly in risk of GI bleeding, is still challenging for the clinician in patients with dyspepsia. In this evidence based case report, it will estimate the precise risk of GI bleeding of SSRI in dyspepsia.

CASE ILLUSTRATION

A woman, 63 years old, was referred from endocrinology clinic to psychosomatic clinic with the chief complaint of sleep disturbances. She admitted of having difficulties to fall asleep and easily wake up since one year ago, when her husband was diagnosed with ischemic stroke. As the only caregiver that her husband had, she felt exhausted and tense to monitor him closely. She also afraid whether her husband had second attack of stroke in the future. The sequelae of his stroke symptoms was gradually improved due to the treatment and physiotherapy.

Around 6 months ago, she felt a progressive lump at the left side of her neck that accompanied with pain while swallowing. She denied any palpitation and weight loss. However, she felt more easily sweating even in the cold places. Neck ultrasonography found multiple thyroid nodule and serum hormon thyroid levels increased from laboratory examination. The thyroid scintigraphy was performed to confirm the ultrasonography (USG) findings and found multiple cold nodule in thyroid. She then proceed the examination to fine needle aspiration biopsy. The histopathology showed benign lesion of thyroid. The doctor prescribed her with methimazole 2.5 mg once daily to control the thyroid hormone levels. She routinely consumed the drug and the last time she checked, her thyroid hormone levels was already at normal range.

Approximately 4 months ago, her husband was diagnosed again with second ischemic stroke. However, in this examination, the clinician found multiple brain aneurysms that could be ruptured anytime. She felt more anxious about her husband disease. However, she could accept the reality of her husband's disease and then hired a care giver to help her. She also claimed to have decreased appetite. She denied any epigastric pain, burning, heartburn, and history of GI bleeding. However, she felt easily full after eating and frequently bloating. The symptoms

persisted even after the doctor prescribed her with proton pump inhibitors dan prokinetic for a month. An endoscopy procedure showed multiple polyp in gaster and mild gastritis. The histopathology of gaster specimen reported non-active, non-atrophy, non-dysplasia reactive gastropathy, and no *H. pylori* was found. She felt the symptoms persisted even after she consumed lansoprazole 20 mg twice daily, sucralfate 10 cc four times daily, and domperidone 10 mg three times daily. Beside the gastrointestinal symptoms, she also complained the sleep problem. She had trouble falling asleep and easily wake up during night. She had hypertension and dyslipidemia since 1 year ago and routinely consumed candesartan 8 mg once daily and atorvastatin 20 mg once daily.

She was then diagnosed with generalized anxiety disorders, insomnia, toxic multinodular goitre, mixed dyspepsia, mild gastritis, hypertension, and dyslipidemia. The doctor planned to give her sertraline 25 mg once daily in the morning and lorazepam 0.5 mg once daily at night. However, the doctor was not really sure about the risk of GI bleeding of sertraline in patients with dyspepsis.

CLINICAL QUESTION

In patients with dyspepsia, does the use of selective serotonin reuptake inhibitor (SSRI) will increase risk of gastrointestinal bleeding?

Table 1. Clinical questions based on PICO

PICO criteria	Variable
Patient/problem	Dyspepsia
Intervention	Selective serotonin reuptake inhibitor (SSRI)
Compare to	Do not receive SSRI
Outcome	Gastrointestinal bleeding

Searching Strategy and Screening Criteria

To answer the aforementioned clinical question, systemic literature searching was performed using several online electronic databases, including PubMed, Cochrane, Scopus, and ProQuest on 11st September 2022. The keywords consisted of "dyspepsia", "selective serotonin reuptake inhibitors", "gastrointestinal bleeding" and their synonyms. We use these three keywords to increase the sensitivity and obtain more related articles.

After the search results were obtained and filter the duplicate articles, screening the title and abstract were performed by using the pre-defined eligibility ciriteria. The inclusion criteria in this report are study design (systematic review or meta-analysis, randomized controlled trial (RCT), and cohort studies); adults (> 18 years old); language restriction (English or Bahasa). Meanwhile, the exclusion criteria in this report are non human studies (laboratory experiment or animal studies).

To determine which papers will be further appraised critically with validated instrument, an extensive reading of full-text articles wil be performed.

Critical Appraisal

The assessment of vailidity, importance, and applicability of each article used the validated critical appraisal tool for meta-analysis, clinical trial, or cohort study. For meta-analysis, critical appraisal was conducted by using FAITH critical appraisal tool. For clinical trial and cohort studies, critical appraisal were performed by using critical appraisal tool from Centre for Evidence-Based Medicine (CEBM) Oxford. Oxford levels of evidence was used to determine the level of evidence of each study.

RESULTS

Of 247 records identified through extensive literature searching from the four major electronic databases, as many as 182 articles were obtained after removing the duplicates. Based on the eligibility criteria, only 3 studies were continued for further review. The reason of excluding several studies included different population (patients who did not have dyspepsia, patients with premature ejactulation, psoriasis), different intervention (other than SSRI), different outcome (weight loss, risk of gastric cacner, gastric function), and different types of study design (review article, case control, erratum). Search queries were further described in Table 2. Flowchart of the searching strategy was presented in Figure 1.

Three articles that included in this study are one RCT study by Talley et al and two cohort studies by Laursen et al and Venerito et al.[14–16] The summary of each study was summarized in Table 3. Talley et al conducted a double-blinded randomized controlled study to assess the efficacy and safety of amitriptyline and escitalopram on functional dyspepsia. As many as 292 patients with functional dyspepsia were involved in this study and randomized into three groups of treatment (placebo, amitriptyline, and escitalopram). One of the secondary outcome was adverse events. Black stool was only found in 1 patient in amitriptylin arm and none in escitalopram or placebo.[14]

Table 2. Search queries, hits, and screened articles

Database	Search Keyword	Hits	Screened Articles
PubMed	(("selective serotonin reuptake inhibitor"[Title/Abstract] OR "selective serotonin reuptake inhibitors"[Title/Abstract] OR "SSRI"[Title/Abstract] OR "fluoxetine"[Title/Abstract] OR "citalopram"[Title/Abstract] OR "escitalopram"[Title/Abstract] OR "paroxetine"[Title/Abstract] OR "fluvoxamine"[Title/Abstract] OR "sertraline"[Title/Abstract]) AND ("dyspepsia"[Title/Abstract] OR "peptic ulcer"[Title/Abstract] OR "duodenal ulcer"[Title/Abstract] OR "gastric ulcer"[Title/Abstract] OR "gastric cancer"[Title/Abstract] OR "reflux esophagitis"[Title/Abstract])) AND (humans[Filter])	85	2
Cochrane	((selective serotonin reuptake inhibitor):ti,ab,kw OR (SSRI):ti,ab,kw OR (fluoxetine):ti,ab,kw OR (citalopram):ti,ab,kw OR (escitalopram):ti,ab,kw OR (paroxetine):ti,ab,kw OR (fluvoxamine):ti,ab,kw OR (sertraline):ti,ab,kw) AND ((dyspepsia):ti,ab,kw OR (peptic ulcer):ti,ab,kw OR (duodenal ulcer):ti,ab,kw OR (gastric ulcer):ti,ab,kw OR (gastric cancer):ti,ab,kw OR (reflux esophagitis):ti,ab,kw)	4	0
Scopus	TITLE-ABS-KEY ("selective serotonin reuptake inhibitor" OR "selective serotonin reuptake inhibitors" OR "SSRI" OR "fluoxetine" OR "citalopram" OR "escitalopram" OR "paroxetine" OR "fluvoxamine" OR "sertraline") AND TITLE-ABS-KEY ("dyspepsia" OR "peptic ulcer" OR "duodenal ulcer" OR "gastric ulcer" OR "gastric cancer" OR "reflux esophagitis") AND TITLE-ABS-KEY ("gastrointestinal bleeding" OR "gastrointestinal hemorrhage" OR "GI bleeding" OR "GI hemorrhage" OR "melena" OR "hematemesis" OR "haematoschezia")	111	2
ProQuest	("selective serotonin reuptake inhibitor" OR "SSRI" OR "fluoxetine" OR "citalopram" OR "escitalopram" OR "paroxetine" OR "fluvoxamine" OR "sertraline") AND ("dyspepsia" OR "peptic ulcer" OR "duodenal ulcer" OR "gastric ulcer" OR "gastric cancer" OR "reflux esophagitis") AND (("gastrointestinal bleeding" OR "gastrointestinal hemorrhage" OR "GI bleeding" OR "GI hemorrhage" OR "melena" OR "hematemesis" OR "haematoschezia"	51	2

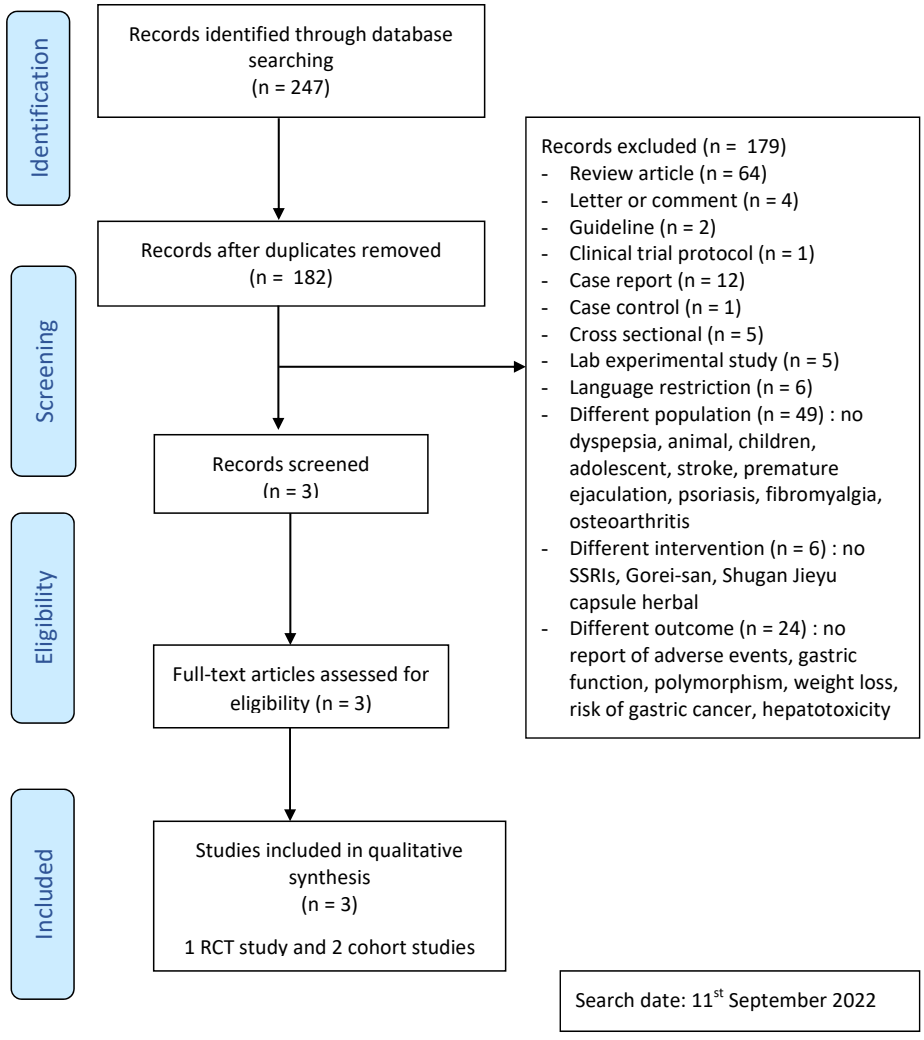

Figure 1. Flowchart of searching strategy

Table 3. Characteristics of included studies

Reference	Study design	Subjects	Determinants	Inclusion criteria	Exclusion criteria	Outcome	LoE
Talley, et al[14] (2015) 2006-2012 Multicenter National Institutes of Health	Double-blinded randomized controlled trial (RCT)	292 patients with functional dyspepsia	Three treatment arms: 1. Placebo 2. Amitryptiline 3. Escitalopram (97 placebo, 97 amitryptiline, 98 escitalopram) for 10 weeks	1. 18–75 years old 2. Fulfill Rome III criteria for functional dyspepsia (FD) 3. Normal endoscopy results within five years	1. Symptom resolution with proton pump inhibitor (PPI) 2. History of esophagitis or ulcer or other organic upper gastrointesinal (GI) disease 3. Current antidepressant or non-steroidal anti-inflammatory drugs (NSAIDs) use 4. Current drug of alcohol abuse 5. Current pregnancy 6. Major illness or abdominal surgery 7. Hospital anxiety and depression scale (HADS) with depression score ≥ 11	Primary outcome: - self-report adequate relief for minimal 50% of weeks 3-12 of treatment Secondary outcome: - gastric emptying test - nutrient drink test - daily diary symptoms - dyspepsia-specific quality of life - adverse events	1B
Laursen, et al[15] (2017) 2006-2014 Danish Clinical Register of Emergency Surgery	Prospective cohort study	14,343 patients who admitted to hospital with peptic ulcer bleeding	SSRI treatment: use of any SSRI at the time of hospitalisation, irrespective of dose	Patients who admitted to hospital with peptic ulcer bleeding during 2006–2014	1. Readmission during the period of inclusion	Primary outcome: endoscopy-refractory bleeding Secondary outcome: rebleeding and 30-day mortality	2B
Venerito, et al[16] (2018) 2004–2014 Otto-van-Guericke University Hospital	Retrospective cohort study	1,719 patients who diagnosed with peptic ulcer disease confirmed by endoscopy (56.9% had peptic ulcer bleeding and 43.1% had uncomplicated)	selective serotonin reuptake inhibitor (SSRI), NSAIDs, antiplatelet, anticoagulant, corticosteroid	No data	No data	Peptic ulcer bleeding	2B

Laursen et al performed a prospective cohort study on patients admitted to hospital with peptic ulcer bleeding during 2006-2014 in Denmark. A total of 14,343 patients were participated in this study. The outcome of the study was endoscopy-refractory bleeding, rebleeding rate, and mortality rate. The rebleeding case was confirmed by endoscopy, surgery, and transcatheter arterial embolization. This study reported no statistically significant of rebleeding rate in SSRIs user compared to non-SSRI user.[15]

Retrospective cohort study by Venerito et al in 2018 involved 1,719 patients who diagnosed with peptic ulcer disease that confirmed by endoscopy. As many as 56.9% patients had peptic ulcer bleeding and 43.1% had uncomplicated peptic ulcer. Several medication (SSRI, NSAIDs, antiplatelet, anticoagulant, corticosteroid) were included in risk factor of GI bleeding analysis. No statistically significant was found between peptic ulcer bleeding and SSRI users.[16] The critical appraisal of selected articles are described in Table 4 and Table 5.

These three studies did not provide strong evidence regarding the effect of SSRI administration on the incidence of gastrointestinal bleeding. According to the evidence, the risk of GI bleeding in SSRIs users with dyspepsia is still unclear.

DISCUSSION

Several studies have reported the increased risk of GI bleeding in patients who consumed SSRIs. Jiang et al in 2014 conducted a systematic review and meta-analysis of controlled observation studies to obtain the risk of upper GI bleeding in SSRI users. As many as 6 cohort and 16 case-control studies were involved in this study. The use of SSRI increased the risk of bleeding as many as 55% (OR = 1.55; 95% CI: 1.35–1.78). In subgroup analysis, concomitant drugs of SSRI with NSAID or antiplatelet further increased the risk of GI bleeding (OR 2.48; 95% CI 1.70–3.61 for antiplatelet and OR = 3.72; 95% CI: 3.01–4.67 for NSAID). The use of acid-suppressing drugs was not statistically significant reducing the risk of GI bleeding (OR = 0.81; 95% CI: 0.43–1.53).[17] Recent meta-analysis by Alam et al in 2022 was conducted to obtain the latest evidence about the risk of upper GI bleeding in patients with concurrent SSRI and NSAID consumption. This study reported similar results with the previous study, which concurrent SSRI dan NSAID use increased the risk of upper GI bleeding with OR = 1.75; 95% CI: 1.32–2.33).[18] However, these two meta-analysis did not elaborate the comorbidities that contribute to GI bleeding risk.

Table 4. Critical appraisal of randomized clinical trial (RCT) study

Title	Validity					Importance	Applicability
	Randomization	Similar between group at start	Equally treated	Entered the trial accounted for	Objective measurement or blinding		
Talley, et al [14] (2015)	Yes	Yes	Yes	Yes	Yes	RR = (0/98)/(1/194) = 0 EER = 0/98 = 0 CER = 1/194 = 0.005 ARR = CER – EER = 0.005 RRR = ARR/CER = 1 NNT = 1/ARR = 194	Yes

RR: relative risk; EER: experimental event rate; CER: control event rate; ARR: absolute risk reduction; RRR: relative risk reduction; NNT: number needed to treat

Table 5. Critical appraisal of cohort study

Title	Validity								Importance	Applicability
	Clearly defined groups	Similar treatment and clinical outcomes	Long and complete follow up	Exposure preceded outcome	Dose-response gradient	Dechallenge-rechallenge study	Consistent from study to study	Biological sense		
Laursen, et al [15] (2017)	Yes	Yes	Yes	Yes	No	No	No	Yes	RR = (250/1,590)/(1,697/10,575) = 1.02 EER = 250/1,590 = 0.157 CER = 1,697/10,575 = 0.1604 ARR = CER – EER = 0.0034 RRR = ARR/CER = 0.021 NNT = 1/ARR = 1/0.0034 = 294	Yes
Venerito, et al [16] (2018)	Yes	Yes		Yes	No	No		Yes	RR = (16/24)/(673/1,148) = 1.13 EER = 16/24 = 0.667 CER = 673/1,148 = 0.586 ARI = EER-CER = 0.667-0.586 = 0.081 NNH = 1/ARI = 1/0.081 = 13	Yes

RR: relative risk; EER: experimental event rate; CER: control event rate; ARR: absolute risk reduction; RRR: relative risk reduction; NNT: number needed to treat; ARI: absolute risk increase; NNH: number needed to harm

A population-based cohort study in Taiwan by Cheng et al in 2015 involved 8,809 SSRI users in 10-year follow up period. SSRI was independently associated with risk of upper GI bleeding (HR = 1.97; 95% CI: 1.67–2.31). Not only upper GI bleeding, the SSRI users also had increased risk of lower GI bleeding (HR = 2.96; 95% CI: 2.46–3.57). In regression analysis to determine the risk factors of both upper and lower GI bleeding in SSRI users, several risk factors including age, sex, hypertension, diabetes, dyslipidemia, coronary artery disease, chronic obstructive pulmonary disease, chronic renal disease, peptic ulcer disease, and medication were adjusted. Uncomplicated peptic ulcer was not associated with GI bleeding in SSRI users. The safety profile of SSRI in patients with dyspepsia is still unknown.[19]

Several mechanism have been proposed to explain the association between the consumption of SSRI with the risk of GI bleeding. The mechanism of action of SSRI in depression is to downregulate serotonin (5-hydroxytryptamine/5-HT) receptors in brain. However, further study found that SSRI also downregulates the receptors in platelet. Most of serotonin is produced by enterochromaffin cells in GI tract. Serotonin is then metabolized by liver and pulmonary vascular endothelium and then stored in blood platelet.[20]

The first mechanism is the inhibition of serotonin enterance into platelet. SSRI works by inhibiting the transport protein in synaptic cleft, resulting the blockage of uptake of synaptic serotonin into the pre-synaptic neuron. This mechanism is also occurred in blood platelet and reported can alter the platelet activity in hemostasis. Abnormality mobilization of calcium inside of the platelet, inhibition of nitric oxide synthase, depletion of the storage of serotonin, reduction of platelet factors secretion in response to stimulation, and reduction of membran receptors that participated in platelet activation, have been reported in several studies. Second, the SSRI have a direct effect to increase gastric acid secretion and become the risk factor of GI bleeding.[20]

Study by Meijer et al in 2004 found that the correlation between the degree of serotonin reuptake inhibition and the bleeding risk. Based on the potency class, antidepressant was classified into 3 groups. There were high (fluoxetine, sertraline, clomipramine, paroxetine), intermediate (venlafaxine, amitryptline, fluvoxamine, imipramine, citalopram), and low (mirtazapine, maprotiline, trazodone, doxepine, bupoprion). Antidepressant with high degree of serotonin reuptake inhibiton increased the risk of bleeding compared to intermediate and low, however the associations were not significantly significant. In subgroup analysis, the risk of hospitalization due to bleeding was found increased 2.6-fold in patients who consumed high degree of inhibition of serotonin reuptake compared to low degree.[21]

Jakubovksi et al in 2016 conducted a systematic review and meta-analysis to confirm the association between dose and therapy response in major depressive disorder. As many as 40 studies (10,039 participants) were included in this study. Higher doses of SSRI were associated with increased efficacy. It is still unclear whether the incidence of bleeding is related with higher doses of SSRI.[22] Shahrbabki et al in 2014 reported two cases that the bleeding occurred with higher doses of sertraline and ceased when the dose was reduced. The dose-effect relationship was found when the sertraline was continued to the previous dose resulting to hemorrhage.[23]

The prevalence of adverse event of SSRI in dyspepsia may be underreported. A randomized controlled trial study by Tan et al in 2012 was performed to evaluate the efficacy and safety of sertraline in functional dyspepsia. This study reported that 24 from 98 patients in sertraline group discontinued treatment at week 8. Most of them were due to no specific reason (41.9%) and adverse event (41.2%). However, this study did not mention specifically about the adverse event, including GI bleeding.[24] Lu et al in 2016 conducted a systematic review and meta-analysis to obtain the efficacy and adverse events of antidepressant in the management of functional dyspepsia. In the subanalysis of adverse events, only three of eight studies reported the adverse events of antidepressant. Compared to placebo, patients in antidepressant arm reported statistically significant higher adverse event (31.6% vs. 20.4%) with RR = 1.64; 95% CI: 1.14–2.35. No serious adverse advent was found in this study.[25]

The risk of bleeding of SSRIs in patients with dyspespsia is still unclear. According to Jiang et al, the escitalopram and citalopram had the highest risk of bleeding with OR = 2.45 (95% CI: 1.35–4.42) and 2.07 (95% CI: 1.47–292), respectively. Fluoxetin had the lowest risk of GI hemorrhage with OR = 1.33 (95% CI: 1.40–2.25).[17] Similar results were reported by Wang et al in 2014, which citalopram (OR = 2.66; 95% CI: 1.16–5.93) had the highest risk and fluoxetine (OR = 1.80; 95% CI: 1.18–2.72) had the lowest risk for GI bleeding. The relationship between dose and the risk of GI bleeding was reported by dividing the doses into

four ranges : < 0.5, 0.5-1, 1-2, and ≥ 2 defined daily doses. There were no difference of doses to risk of GI bleeding with OR = 2.23, 2.47, 1.59, 1.75 for < 0.5, 0.5-1, 1-2, and ≥ 2 defined daily doses, respectively. However, all of these findings were not specifically in patients with dyspepsia.[26] Lee et al in 2020 considered to use of proton pump inhibitor (PPI) when prescribing SSRIs to reduce the bleeding risk. This study reported the risk of upper GI bleeding was higher in patients consumed concurrent NSAIDs or SSRIs without PPI. The adjusted OR for NSAID and SSRI were 2.47; 95% CI: 1.26–4.83 and 10.8; 95% CI: 2.41–48.1). This is the first systematic review to determine the risk of GI bleeding in patients with dyspepsia. The limitation of this study are the restriction of language and the searching is only conducted in online electronic databases.[27]

CONCLUSION

According to extensive literature searching, the risk of GI bleeding of SSRIs in patients with dyspepsia is still unclear. The concurrent use of SSRIs with nonsteroidal antiinflammatory or antiplatelet drugs ~~anticoagulant~~ increased the risk of GI bleeding.

PPIs could reduce the risk of GI bleeding, however the use of SSRIs in organic dyspepsia should be avoided. Controlled trials with larger sample sizes in patients with dyspepsia are recommended to quantify the risk of GI bleeding.

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