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Impact of selective serotonin receptor inhibitors on gastric histopathology in patients with depression

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ABSTRACT

Objective: Antidepressant medications such as Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) are used in the psychopharmacological treatment for various types conditions. This study aimed to investigate whether SSRIs and SNRIs could reduce gastric intestinal metaplasia.

Material Methods: A total of 212 patients who underwent upper gastrointestinal endoscopy plus biopsy in our clinic and were using selective serotonin reuptake inhibitors and other potent serotonin reuptake inhibitors were included in the study. A control group was created with a total of 230 age and gender matched patients who underwent upper gastrointestinal endoscopy plus biopsy but had no SSRI or SNRI usage. Patients' endoscopic and pathologic findings were recorded retrospectively and compared between the groups.

Results: The patient group consisted of 180 (84.9%) male and 32 (15.1%) female patients, while the control group included 175 (76.1%) male and 55 (23.29%) female patients. There was a statistically significant difference between the groups in terms of gender (p=0.020). The rates of erythematous antral gastritis (p<0.001), peptic ulcer (p=0.019), erosive gastropathy (p=0.001) and duodenitis (p=0.002) were statistically significantly lower in the patient group compared to the control group. The rates of H.Pylori(p=0.002), intestinal metaplasia (p=0.013), neutrophil activity (acute inflammation) (p<0.001) and chronic inflammation (p<0.001) were lower in the case group compared to the control group.

Conclusion: SSRIs/SNRIs may potentially be used in treating gastrointestinal inflammation and metaplasia. However, further prospective randomised studies with larger series are needed to support our findings.

Keywords: SSRI, SNRI, gastrointestinal tract, H.pylori, inflammation, intestinal metaplasia

INTRODUCTION

Antidepressant medications such as Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) are used in the psychopharmacological treatment for various types of chronic pain, including tension-type and migraine-type headaches, neuropathic pain, fibromyalgia, low back pain or osteoarthritis pain, mood disorders such as major depressive disorder, anxiety disorders such as social anxiety disorder, and sleep disorders such as insomnia (1). SSRIs and SNRIs are the first-line pharmacotherapy for most patients with depression because they are effective and generally better tolerated when compared to other antidepressants (2).

Antidepressant prescription rates are increasing (3), and second-generation antidepressants, including SSRIs and SNRIs are among the most prescribed antidepressants (4). Therefore, effects and side effects of these drugs should be further investigated.

SSRIs and SNRIs are known to increase the amount of serotonin in the central nervous system by blocking or delaying the serotonin reuptake by the nerves. SSRIs and SNRs selectively increase the transmission of serotonin and noradrenaline by inhibiting only serotonin and also noradrenaline reuptake, respectively, resulting in a decrease in the number and sensitivity of postsynaptic receptors (1).

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SSRIs and SNRIs have various side effects on the gastrointestinal system. Serotonin is present in the gastrointestinal mucosa enterochromaffin cells and within neurons in the enteric nervous system. As an enteric neurotransmitter, serotonin initiates peristaltic reflexes, inhibits gastric acid secretion, stimulates the production and release of gastric and colonic mucus, and influences gastrointestinal blood flow (5). Therefore, some of the most frequently reported gastrointestinal system-related effects, such as nausea, vomiting, diarrhoea, constipation, dyspepsia, and abdominal pain, related to increased serotonin may occur, especially at the beginning of the treatment with SSRIs and SNRIs (4).

Either enteric or colonic mucosal immigration characterises gastric intestinal metaplasia (GIM) into the gastric mucosa (6). GIM is prevalent in subjects who live in Asia and could lead to gastric carcinoma at a rate of almost 1% annually. GIM is considered a precancerous lesion, increasing the risk of developing gastric cancer by 6-fold (7). Characteristics of the at-risk population for developing GIM include white race, obesity, and gastroesophageal reflux disease (GER) (8). Factors such as insufficient esophageal peristalsis, delayed gastric emptying and antroduodenal motility disorders and increased acid secretion play a role in the pathophysiology of GER (9).

This study aimed to investigate whether SSRIs and SNRIs could reduce gastric intestinal plasia.

MATERIAL and METHODs

Before the beginning, the study protocol was approved by the local ethics committee of our hospital with January 2019 dated and 2019/1/9 numbered decision.. Informed consent was waived because of the retrospective nature of the study. This study was conducted in line with the ethical principles of the declaration of Helsinki.

A total of 212 patients who underwent upper gastrointestinal endoscopy plus biopsy in our clinic and were using selective serotonin reuptake inhibitors and other potent serotonin reuptake inhibitors between 2017 and 2019 were included in the study. Patients who were confirmed to have been using antidepressants regularly for at least 6 months by the national health information network (MEDULA) pharmacy database were included in the study. Patients with hepatic and renal failure, those with rheumatic disease, diagnosis of malignancy, patients with primary immune insufficiency, those using immunosuppressive and aspirin-antithrombotic drugs, patients who underwent gastric surgery and those who had received H. pylori eradication therapy previously were excluded from the study.

Patients' demographic data such as age and gender, endoscopic and histopathologic findings were recorded. In addition, duration of SSRI/SNRI usage and the drugs used were recorded. Endoscopic findings included the presence of esophagitis, erythematous antral gastritis, erythematous pangastritis, gastric polyps, peptic ulcer, gland polyps, erosive gastropathy and duodenitis. The histopathological results evaluated according to Sydney classification were included in the study. Histopathological findings included the presence of H.pylori, intestinal metaplasia, (focal, complete, and incomplete), gastric dysplasia, gastric neoplasia, neutrophil activity (acute inflammation), and chronic inflammation. Data used in this study was obtained from the electronic database of the hospital and patient files.

A control group was created with a total of 230, age and gender-matched patients who underwent upper gastrointestinal endoscopy plus biopsy, but who had no SSRI or SNRI usage.

Statistical Analysis

Data obtained in this study were statistically analyzed using the SPSS version 22.0 (Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) software. Among the descriptive statistics, categorical variables are expressed as number and percentage, while continuous variables are given as mean ± standard deviation. The normality of the continuous variables was evaluated using the Kolmogorov-Smirnov/Shapiro-Wilk tests and visual (histogram and probability charts). Normally distributed variables were compared with the independent t-test and non-normally variables with the Mann-Whitney test between the two groups. Categorical variables were compared using Pearson's Chi-square ($\chi 2$) test. In Pearson Chi-square analysis, results are presented with Odds Ratio (OR) and 95% Confidence interval. $p<0.05$ values were considered statistically significant.

RESULTs

This study included 212 cases who had undergone EGD (esophagogastroduodenoscopy) and biopsy due to dyspeptic complaints and had been using the regular antidepressive treatment for at least 6 months, and a control group of 230 people with similar age and gender characteristics. The patient group consisted of 180 (84.9%) male and 32 (15.1%) female patients, while the control group included 175 (76.1%) male and 55 (23.29%) female patients. There was a statistically significant difference between the groups in terms of gender (p=0.020). The most commonly used SSRI was Essitalopram, followed by Sertraline and Paroxetine. Distribution of the patients according to the active ingredients of the antidepressant drugs is given in Table 1 and Figure 1.

Table 1. Demographic data on the use of antidepressants in the patient group

	(n)	(%)
Duration of drug usage		
< 1 year	77	36.3
≥ 1 year	135	63.7
Active ingredient		
Escitalopram-SSRI	42	19.8
Sertraline-SSRI	41	19.3
Paroxetine-SSRI	25	11.8
Venlafaxine-SNRI	22	10.4
Duloxetine-SNRI	18	8.5
Fluoxetine-SSRI	17	8.0
Citalopram-SSRI	10	4.7
Trazodone-YELLOW	6	2.8
Milnacipran-SNRI	2	0.9
Fluvoxamine-SSRI	1	0.5
Mirtazapine-NASSA	1	0.5
Unknown	27	12.7

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Considering the endoscopic findings; the rates of erythematous antral gastritis (p<0.001), peptic ulcer (p=0.019), erosive gastropathy (p=0.001), and duodenitis (p=0.002) were statistically significantly lower in the patient group compared to the control group. Accordingly, the probability of erythematous antral gastritis increased by 2.5 folds, peptic ulcer by 3.6 folds, erosive gastropathy by 3.4 folds and duodenitis by 1 fold.The relationship between antidepressant usage and "Endoscopic Findings" is given in Table 2 and Figure 2.

Considering the pathologic findings; the rates of H.Pylori(p=0.002), intestinal metaplazi (p=0.013), neutrophil activity (acute inflammation) (p<0.001) and chronic inflammation (p<0.001) were lower in the case group compared to the control group. Accordingly, the probability of H.Pylori increased by 1.8 folds, intestinal plasia by 1.8 folds, neutrophil activity by 2.1 folds and chronic activity by 7 folds. The relationship between antidepressant usage and "Pathologic Findings" is given in Table 3 and Figure 2.

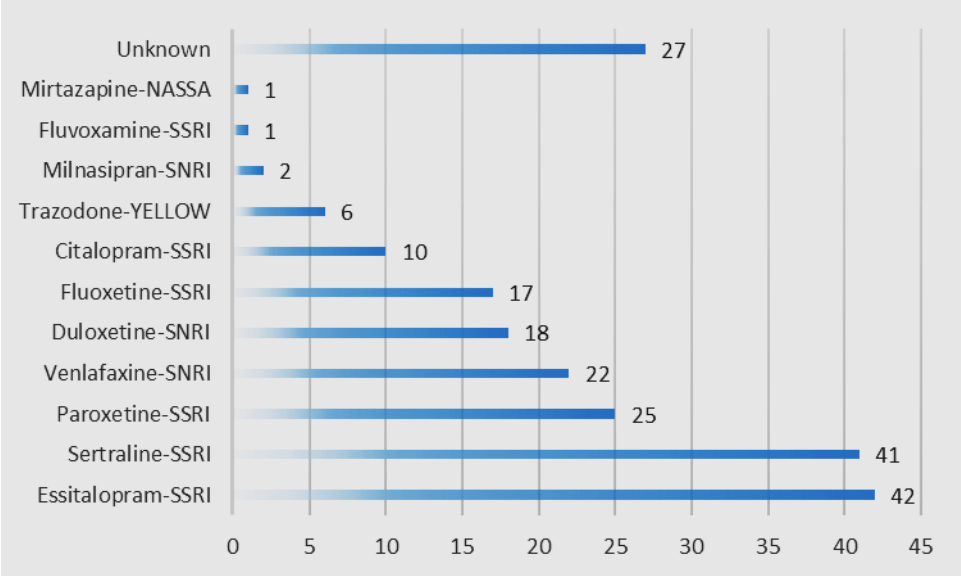

Figure 1. Distribution of active ingredients of the drugs used

Table 2. Endoscopic findings

	Case (n:212)	Control (n:230)	p	AOR	95%CI
Esophagitis					
Yes	58 (27.4)	70 (30.4)	0.476[b]		
No	154 (72.6)	160 (69.6)			
Erythematous antral gastritis					
Yes	70 (33.0)	128 (55.7)	**<0.001[b]**	**2.544**	**1.730-3.745**
No	142 (60.3)	102 (44.3)			
Erythematous Pangastritis					
Yes	52 (24.5)	63 (27.4)	0.493[b]		
No	160 (75.5)	167 (72.6)			
Gastric polyps					
Yes	9 (4.2)	5 (2.2)	0.214[b]		
No	203 (95.8)	225 (97.8)			
Peptic ulcer					
Yes	4 (1.9)	15 (6.5)	**0.019[c]**	**3.623**	**1.111- 3.623**
No	133 (97.8)	368 (95.2)			
Gland polyps					
Yes	7 (3.3)	5 (2.2)	0.466[b]		
No	205 (96.7)	225 (97.8)			
Erosive gastropathy					
Yes	9 (4.2)	30 (13.0)	**0.001[b]**	**3.378**	**1.567-7.692**
No	203 (95.8)	200 (87.0)			
Duodenitis					
Yes	0 (0)	10 (4.3)	**0.002[c]**	**1.044**	**1.017-1.074**
No	212 (100)	220 (95.7)			

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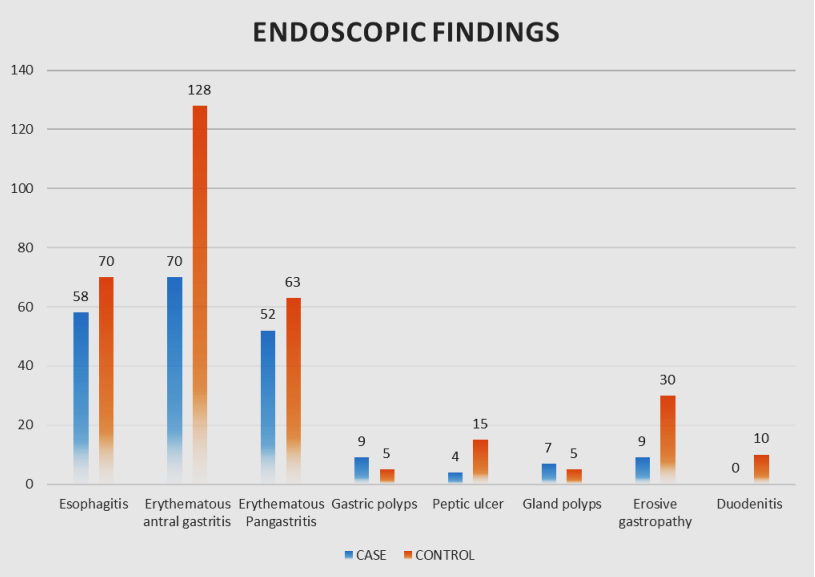

Figure 2. Endoscopic findings of the groups

Table 3. Pathologic findings

	Case	Control	p	AOR	95% CI
H.Pylori	n (%)	n (%)			
Yes	90 (42,2)	132 (57,4)	**0,002**[a]	**1,824**	**1,251-2.666**
No	122 (57,5)	98 (42,6)			
Intestinal metaplasia					
Yes	34 (16,0)	59 (25,7)	**0,013**[a]	**1,805**	**1,127-2,890**
No	178 (84,0)	171 (74,3)			
IM focal					
Yes	7 (3,3)	8(3,5)	0,919[a]		
No	205 (96,7)	222 (96,5)			
IM Complete					
Yes	6 (2,8)	3 (1,4)	0,331[b]		
No	206 (97,2)	217 (98,6)			
IM Incomplete					
Yes	0 (0,0)	1 (0,5)	1[b]		
No	212 (100)	218 (99,5)			
Atrophic gastritis					
Yes	40 (18,9)	50 (21,7)	0,454[a]		
No	172 (81,1)	180 (78, 3)			
Gastric dysplasia					
Yes	0 (0)	5 (2,2)	0,062[b]		
No	212 (100)	225 (97,8)			
Gastric neoplasia					
Yes	0 (0)	1 (0,2)	1[b]		
No	212 (100)	229 (99,7)			
Neutrophil activity (acute inflammation)					
Yes	86 (40,6)	136 (59,1)	**<0,001**[a]	**2,118**	**1,449-3,095**
No	69 (50,7)	147 (37,7)			
Chronic Inflammation					
Yes	139 (65, 6)	214 (93,0)	**<0,001**[a]	**7,042**	**12,50-3,921**
No	73 (34,4)	16 (7,0)			

DISCUSSION

In the present study, we investigated the effects of SSRIs/SNRIs on gastric histopathology in patients with depression for the first time in the literature. We found that, SSRIs/SNRIs may decrease the risk of developing gastrointestinal metaplasia.

In the brain, selective serotonin reuptake inhibitors (SSRIs) are known to downregulate serotonin (5-hydroxytryptamine [5HT]) receptors and used to treat depressive diseases amid elevated serotonin levels (10). Enterochromaffin cells in the gastrointestinal system are the major source of 5HT. After being produced and released into the GI tract, 5HT is captured by platelets and metabolized by the liver or pulmonary vascular endothelium (11).

Serotonin has key roles in the central nervous system, including brain development, sleep, mood, and appetite, and these effects are also closely related to the gut system, also called gut-brain axis (12). At another perspective, serotonin-secreted enterochromaffin (EC) cells in the intestinal mucosa have reportedly determined a number of gastrointestinal functions including peristalsis, secretion, vasodilation, and perception of pain or nausea. In our study, erythematous antral gastritis, peptic ulcers, erosive gastropathy and duodenitis were significantly lower in the patients who received SSRIs/SNRIs compared to the control group, suggesting the role of serotonin in endoscopic findings of patients with depression.

A recent study involving patients who had been treated both aspirin and SSRIs amid their depressive diseases showed that inhibition of serotonin reuptake into neurons and platelets caused a damage on platelet accumulation (13). It has also been reported that SSRI users have experienced more gastrointestinal bleeding attacks due to increased gastric acid secretion and the inhibition of serotonin's access into platelets (14). Dall et al. suggested an association between SSRIs and uncomplicated peptic ulcers (15).

On the other hand, in a study by Laursen et al., the use of selective serotonin receptor inhibitors (SSRIs) was not associated with increased risk of endoscopy-refractory bleeding, rebleeding or mortality in peptic ulcer bleeding (16). Similarly, in our study, we did not observe endoscopy-refractory bleeding, and the rate of peptic ulcers was low in the patients receiving SSRIs.

Erythematous pangastritis and antral nodularity on endoscopic findings had a correlation with H. pylori positivity (17). In the present study, the rate of H. pylori was lower in the patients receiving SSRIs/SNRIs whose erythematous pangastritis and antral nodularity was also lower compared to the control group, consistent with the literature.

In the present study, considering pathological findings; the rates of H.Pylori ($p=0.002$), intestinal metaplazi ($p=0.013$), neutrophil activity (acute inflammation) ($p<0.001$), and chronic inflammation ($p<0.001$) were lower in the case group compared to the control group. The probability of H.Pylori increased by 1.8 folds, intestinal plasia by 1.8 folds, neutrophil activity by 2.1 folds, and chronic activity by 7 folds in patients with gastrointestinal pathologies who have not been receiving SSRIs/SNRIs.

Dall et al. claimed that H. pylori infection increases the risk of SSRI-related serious upper gastrointestinal bleeding (UGB) (15). Our study did not observe an association between H.pylori and UGB.

GIM is an important precursor lesion in the pathway to gastric cancer (GC), and regional prevalence of GIM correlates closely with the incidence of GC worldwide (18). Gastrointestinal metaplasia (GIM) results from diverted differentiation of gastric stem cells towards cells of the small intestine or colonic phenotypes.

The presence of mucin-containing, intestinal-type, goblet cells, absorptive cells and Paneth cells characterizes it. Risk factors of GIM have been reported as the presence of H. pylori infection, older ages, smoking history, strong spicy food, occupation status, and IL10-592 C/A (19). In our study, the lower rate of H.pylori was in parallel with the low rate of GIM in patients receiving SSRIs/SNRIs. In addition, low rates of acute and chronic inflammation in the patient group receiving SSRIs/SNRIs may explain the low rate of GIM.

Our findings indicate lower rates of H.pylori, acute and chronic inflammation and GIM, in the patients receiving SSRIs/SNRIs, suggesting that these drugs may have the potential for treatment of these conditions. However, since there is no study regarding effects of the use of these agents on gastric histopathology, we could not compare our results exactly.

Study Limitations

Main limitations of this study include its retrospective nature and being conducted in a single center. However, the number of patients is relatively large and this study is the first to investigate the effects of antidepressants on gastrointestinal histopathology.

CONCLUSION

The rates of erythematous antral gastritis, peptic ulcer, erosive gastropathy, duodenitis, H.Pylori, gastrointestinal metaplazi, neutrophil activity (acute inflammation) and chronic inflammation were significantly lower in patients receiving SSRIs/SNRIs compared to those who have not been using these drugs, suggesting that these agents may have the potential for using in the treatment of gastrointestinal inflammation and metaplasia. However, further prospective randomised studies with larger series are needed to support our findings.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical

standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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