HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

ISSN 2334-9492 (Online)

Hospital Pharmacology. 2026; 13(1):1765-1772

UDC: 615.214.3.065; 616.34-009.1

doi:10.5937/hpimj2601765K

Original Study

Analysis of Signals For Constipation Among Antidepressants: Using FDA Adverse Event Reporting Database

Milanjot Kaur, Kunal Choudhary, Slobodan M. Janković

Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

SUMMARY

Introduction: It is estimated that 43% of patients with major depressive disorder discontinue pharmacotherapy due to adverse effects. Evidence suggests antidepressant users may experience constipation. Hence, evaluating the gastrointestinal safety profile of these medications is important, as chronic gastrointestinal conditions can negatively affect quality of life, reduce work productivity, and increase overall health risks.

Aim: The aim of the study was to evaluate potential signals of constipation linked to antidepressants in publicly accessible databases, which contain spontaneous reports of adverse drug events.

Material and Methods: This secondary research study utilized publicly accessible pharmacovigilance databases including the Food and Drug Administration Adverse Event Reporting System (FAERS), VigiBase accessed via the VigiAccess portal, and the EudraVigilance database established by the European Medicines Agency. Disproportionality analyses for constipation were conducted using the reporting odds ratio (ROR), Yule's Q, proportionality reporting ratio (PRR), and information component (IC).

Results: Among antidepressants, the strongest signals for constipation in descending order were nortriptyline (ROR=8.89), nefazodone (ROR=4.21), amitryptyline (ROR=4.05), trimipramine (ROR=4.01), amoxapine (ROR=3.96), fluvoxamine (ROR=3.74) and duloxetine (ROR=3.63). Antidepressants with weak signals were escitalopram, fluoxetine, sertraline , agomelatine, bupropion, desvenlafaxine and milnacipran.

Conclusion: Clinicians must consider a patient's pre-existing risk factors for constipation and be aware that antidepressants differ in their tendency to cause constipation. Hence, antidepressants with the lowest chance of causing constipation, such as escitalopram, fluoxetine, sertraline, and bupropion - may be preferred.

Keywords: Antidepressants, Constipation, Adverse Event, Spontaneous Reporting, Disproportionality Measures

INTRODUCTION

Constipation is a symptom or condition that involves difficulty and infrequent bowel movements, usually three or fewer times a week. It is among the most common digestive issues in the United States and a frequent reason for referrals to colorectal surgeons and gastroenterologists[1-6].

Constipation can be broadly classified into primary and secondary forms. Functional constipation and irritable bowel

Corresponding author:
Professor, Primarius Slobodan M. Janković, MD, PhD
Specialist in Clinical Pharmacology
Department of Pharmacology and Toxicology, Faculty of Medical Sciences, Svetozara Markovića 69, 34000 Kragujevac, Serbia
E-mail: sjankovic@fmn.kg.ac.rs

syndrome with predominant constipation are included in the former, while drug-induced constipation (DIC), various diseases (symptomatic constipation), and colonic disorders (constipation brought on by organic diseases) are associated with the latter. Drug-induced constipation (DIC) is responsible for about 11% of all occurrences of treated constipation, according to a retrospective study conducted using a Japanese claims database [6].

A wide range of medications may contribute to constipation, including diuretics, opioid analgesics, anxiety medications, and antiemetics[2]. Opioid-induced constipation (OIC) is the most representative DIC and globally well-known. According to a cross-sectional analysis of depersonalized data from the German Pain e-Registry, DIC was a common comorbidity in one-third of patients receiving pain treatment [3].

Constipation associated with antidepressants use is frequently underreported. However, gastrointestinal adverse effects are among the most commonly observed side effects of these medications [4]. In a study evaluating the 30 drugs most frequently associated with DIC, duloxetine—a serotonin–norepinephrine reuptake inhibitor—ranked 26th, accounting for 0.57% of reported cases [5]. According to an article published in the Journal of Cellular and Molecular Medicine, Inhibition of TRPC4 channel activity in colonic myocytes by tricyclic antidepressants disrupts colonic motility, causing constipation [6].

One study examining selective serotonin reuptake inhibitors (SSRIs) in patients with depression found that sertraline was associated with the highest probability of digestive system adverse effects [7]. Similarly, an Italian-based study on Gastrointestinal side effects associated with antidepressant treatments in patients with major depressive disorder indicated that escitalopram and sertraline were shown to be the least tolerated antidepressants on the gastrointestinal tract [8]. However, these data do not confirm whether these medications specifically cause constipation, nor do they identify which gastrointestinal symptoms predominate.

Current evidence does not allow for reliable comparison of antidepressants with respect to their risk of inducing constipation, leaving clinicians uncertain about which antidepressant to transition to when a patient experiences constipation during mental health treatment.

AIM

The objective of our study was to examine the frequency of constipation reports in publicly accessible databases of spontaneous reports of adverse drug events and explore the potential signals of constipation associated with antidepressants, providing a foundation for comparing antidepressants according to their associated risk of unpleasant adverse effect.

MATERIAL AND METHODS

This non-commercial academic Phase IV no interventional study was based on spontaneous reports of adverse drug events obtained from three publicly accessible pharmacovigilance databases: the Food and Drug Administration (FDA): the FDA Adverse Event Reporting System (FAERS) Database [9], VigiBase accessed via the World Health Organization's (WHO) VigiAccess portal [10], and the EudraVigilance database created by the European Medicines Agency (EMA) [11]. As soon as the first reports of antidepressants appeared in the databases, the data was collected. The antidepressants listed below were looked into: Sertraline, Vilazodone, Vortioxetine, Citalopram, Escitalopram, Fluxetine, Fluvoxamine, Paroxetine, Duloxetine, Desvenlafaxine, Milnacipran, Venlafaxine, Levomilnacipran, Nefazodone, Trazodone, Clomipramine, Imipramine, Amitriptyline, Doxepin, Trimipramine, Amoxapine, Nortriptyline, Mirtazapine, Desipramine, Maprotiline, Protriptyline, Isocarboxazid, Tranylcyclopromine, Phenelzine, Moclobemide, Bupropion, Agomelatine.

Disproportionality analysis was performed to identify potential safety signals for the adverse event „constipation". A two-by-two contingency table was constructed for each drug–event pair, and the following indices were calculated: reporting odds ratio (ROR), Yule's Q, proportional reporting ratio (PRR), and information component (IC) (IC)[12].

A signal was considered statistically significant if all of the following criteria were met: [1] the lower bound of the confidence interval for ROR is greater than 1 and there are more reports than 5; [2] the value for Yule's Q is greater than 0.8; [3] the lower bound of the confidence interval for PRR is greater than 1 and there are more reports than 5; and [4] the

Table 1. Number of reported cases of constipation associated with antidepressants

NAME OF DRUG (year of first report)	VIGIBASE DATABASE	EUDRAVIGILANCE
Amitriptyline (1969)	2439	481
Duloxetine (2005)	1948	664
Escitalopram (2003)	1715	239
Venlafaxine (1998)	1197	568
Bupropion (1988)	1004	200
Paroxetine (1993)	879	301
Sertraline (1997)	831	313
Fluoxetine (1997)	788	173
Mitrazapine (1996)	578	256
Nortriptyline (1995)	544	132
Desvenlafaxin (2008)	489	70
Vortioxetine (2024)	473	166
Imipramine (1969)	436	31
Trazodone (1993)	425	158
Clomipramine (1986)	336	119
Citalopram (1998)	324	194
Milnacipran (2007)	167	35
Fluvoxamine (1984)	124	53
Nefazodone (2001)	106	-
Doxepin (1981)	99	41
Agomelatine (2009)	55	34
Amoxapine (1977)	50	9
Vilazodone (2011)	38	-
Trimipramine (1986)	37	22
Tranylcypromine (1985)	15	10
Maprotiline (1980)	62	34
Desipramine (1994)	52	2
Isocarboxazid (1970)	3	1
Phenelzine (1985)	61	11
Moclobemide (1996)	22	4
Levomilnacipran (2013)	32	-
Protriptyline (2010)	10	-

value for IC is positive and the lower bound of the confidence interval is greater than zero. Based on each drug's contingency table, the Chi square was also computed. The threshold value of probability for rejecting the null hypothesis was 0.01. The number of constipation reports for all antidepressants investigated are shown in the Table 1 for Vigiaccess and Eudravigilance databases. The number of constipation reports from FAERS database and disproportionality measures are shown in the Table 2.

RESULTS

Table 1 presents data from the VigiAccess and EudraVigilance databases, including the number of constipation reports for each antidepressant and the total number of adverse event reports. Antidepressants are listed in descending order according to the number of constipation reports. Since the other two databases do not provide access to the total number of specific adverse event reports involving all drugs, values of disproportionality measures were computed solely using the FAERS database from 1968 to the present. Table 1 summarizes the absolute number of constipation reports across all 32 antidepressants. The highest raw report counts were observed foramitriptyline, duloxetine, escitalopram, venlafaxine, and bupropion, reflecting their widespread use.

Table 2. The disproportionality analysis of FAERS database

Reporting Odds Ratio (ROR) = (a/c)/(b/d)
Yules Q ratio = (ad-bc)/(ad+bc)
Proportional Reporting Ratio (PRR) = (a/(a+c))/(c/(c+d))
Information Component (IC) = log2(p(x,y))/(p(x)p(y))

Name of drug (year of first report)	No of cases	Reporting odds ratio		Proportional reporting ratio		Information component		Yules Q ratio		
		ROR	CI	PRR	CI	IC	CI	Yules Q	CI	Chi square
Nortriptyline (1995)	267	8.89	1.1	0.17	0.02	3.07	1.17	0.79	0.02	0.000
Nefazodone (2001)	6	4.21	3.81	0.004	0.003	2.04	0.17	0.61	0.25	0.000
Amitriptyline (1969)	551	4.05	0.34	0.35	0.02	1.98	0.12	0.6	0.02	0.000
Trimipramine (1986)	17	4.01	2.01	0.01	0.005	1.97	0.69	0.06	0.15	0.000
Amoxapine (1977)	51	3.96	1.11	0.03	0.009	1.97	0.4	0.59	0.08	0.000
Duloxetine (2005)	397	3.63	0.36	0.28	0.02	1.83	0.14	0.56	0.03	0.000
Fluvoxamine (1984)	60	3.74	0.97	0.03	0.009	1.87	0.36	0.57	0.08	0.000
Imipramine (1969)	43	2.88	0.88	0.02	0.008	1.51	0.43	0.48	0.11	0.000
Clomipramine (1986)	55	2.81	0.75	0.03	0.009	1.47	0.38	0.47	0.1	0.000
Vortioxetine (2024)	11	2.63	1.67	0.03	0.02	1.37	0.86	0.44	0.23	0.000
Vilazodone (2011)	06	2.42	2.17	0.004	0.004	1.26	1.16	0.41	0.32	0.026
Doxepin (1981)	59	2.22	0.57	0.03	0.009	1.13	0.37	0.37	0.1	0.000
Trazodone (1993)	237	2.15	0.27	0.15	0.01	1.09	0.18	0.36	0.05	0.000
Mitrazapine (1996)	579	2.01	0.16	0.37	0.03	0.99	0.11	0.33	0.03	0.000
Venlafaxine (1998)	378	1.97	0.2	0.25	0.02	0.97	0.14	0.36	0.04	0.000
Agomelatine (2009)	14	1.89	1.04	0.01	0.005	0.91	0.76	0.3	0.23	0.015
Milnacipran (2007)	6	1.87	1.68	0.004	0.003	0.9	0.16	0.3	0.35	0.118
Citalopram (1998)	403	1.78	0.17	0.26	0.02	0.82	0.14	0.28	0.04	0.000
Desvenlafaxin (2008)	14	1.59	0.88	0.01	0.005	0.67	0.75	0.23	0.24	0.010
Paroxetine (1993)	188	1.66	0.24	0.12	0.01	0.72	0.2	0.24	0.06	0.000
Bupropion (1988)	204	1.44	0.19	0.13	0.01	0.52	0.19	0.18	0.06	0.000
Sertraline (1997)	363	1.24	0.12	0.23	0.02	0.3	0.14	0.1	0.05	0.000
Escitalopram (2003)	167	1.21	0.18	0.11	0.01	0.28	0.21	0.09	0.07	0.010
Fluoxetine (1997)	201	1.05	0.14	0.13	0.01	0.07	0.2	0.02	0.06	0.484
Tranylcypromine (1985)	4	-	-	-	-	-	-	-	-	-
Maprotiline (1980)	4	-	-	-	-	-	-	-	-	-
Desipramine (1994)	3	-	-	-	-	-	-	-	-	-
Isocarboxazid (1970)	3	-	-	-	-	-	-	-	-	-
Phenelzine (1985)	2	-	-	-	-	-	-	-	-	-
Moclobemide (1996)	1	-	-	-	-	-	-	-	-	-
Levomilnacipran (2013)	0	-	-	-	-	-	-	-	-	-
Protriptyline (2010)	0	-	-	-	-	-	-	-	-	-

At the other extreme, levomilnacipran and protriptyline had zero reports, while several MAOIs and older agents had very few.

Table 2 displays the number of constipation reports along with the disproportionality measures with 95% confidence intervals. Once more, the antidepressants are arranged in descending order based on the number of constipation reports. Data extraction was performed independently by all authors on November 27, 2025, using the search term „constipation", and the final dataset was consolidated by the last author. This Table identifies which drugs show a statistically meaningful signal, independent of prescribing frequency. The strongest signals (highest ROR) were for nortriptyline, followed by nefazodone, amitriptyline, trimipramine, amoxapine, fluvoxamine, and duloxetine — all with ROR values above the significance threshold and confirmed by PRR, IC, and Yule's Q. Drugs at the lower end — sertraline, escitalopram, fluoxetine, bupropion, desvenlafaxine, agomelatine, and milnacipran — showed weak or no significant signals. Several drugs (tranylcypromine, maprotiline, desipramine, iso-

carboxazid, phenelzine, moclobemide, levomilnacipran, protriptyline) had too few reports for disproportionality analysis.

DISCUSSION

The present study analyzed constipation-related adverse event signals across a broad range of antidepressants using spontaneous reporting data from three major pharmacovigilance databases. Among 32 antidepressants, the drugs that have the strongest signal for constipation, with more than 10 reports in the databases, were in descending order: Nortriptyline, Nefazodone, Amitriptyline, Timipramine, Amoxapine, Duloxetine, and Fluvoxamine. Among the antidepressants with 0 no of reports for constipation were Levomilnacipran and protriptyline; however, among the antidepressants with fewer than 10 reports and insufficient signals were Vilazodone, Milnacipran, Tranylcypromine, Maprotiline, Desipramine, Isocarboxazid, Phenelzine, Moclobemide except Nefazodone which instead of having only 6 reported cases showed a stronger signal for constipation. Disproportionality analysis revealed a clear hierarchy of constipation risk among antidepressants, with tricyclic agents — particularly tertiary amines — consistently displaying the strongest signals, while most selective serotonin reuptake inhibitors and atypical antidepressants clustered at the lower end of the signal spectrum. Notably, certain drugs generated a disproportionately high signal despite having a relatively modest number of absolute reports, underscoring the importance of using disproportionality measures rather than raw report counts alone when assessing drug safety signals. Conversely, several widely prescribed antidepressants accumulated a large volume of constipation reports in absolute terms, likely reflecting their high global utilization rather than an inherently elevated constipation risk. Taken together, these findings demonstrate that antidepressants differ substantially in their propensity to induce constipation, with important implications for drug selection in patients who are at elevated baseline risk for this adverse effect.

To date, the literature includes several systematic and narrative reviews, as well as analyses of national databases of spontaneous reports of adverse drug events, which have found some association of several antidepressants with constipation. The majority of previous studies indicate that tricyclic antidepressants directly cause a group of symptoms known as anticholinergic side effects, including constipation, by antagonistically interacting with the histamine H1, adrenoreceptor, and muscarinic acetylcholine receptor [15]. Nortriptyline causes constipation by inhibiting acetylcholine action and raising norepinephrine levels in synapses. Additionally, it suppresses histamine activity, which can exacerbate constipation by reducing movement and slowing transit [13].

While secondary amines like desipramine and protriptyline show increased inhibition of norepinephrine uptake, tertiary amines like amitriptyline, clomipramine, doxepin, imipramine, and trimipramine usually show considerable serotonin reuptake inhibition. Although tertiary amine TCAs considerably reduce serotonin absorption, their high rates of constipation are caused by muscarinic receptor antagonism rather than serotonergic action. Secondary amine TCAs, which predominantly block norepinephrine reuptake, exhibit a lower anticholinergic burden and, as a result, a decreased incidence of constipation, however sympathetic-mediated slowing of gastrointestinal motility may still be involved [14]. These observations are in agreement with our findings, in which desipramine and protriptyline were associated with fewer than five reported cases and did not generate significant signals, whereas tertiary amines demonstrated higher numbers of reports and stronger signals for constipation.

Nefazodone acts as an antagonist at 5-HT2 receptors and inhibits 5-HT reuptake to increase serotonin (5-hydroxytryptamine [5-HT]) synaptic transmission. Together, these two processes may increase 5-HT1A-mediated transmission by reducing intestinal motility and enteric neuronal activity, thereby increasing the risk of constipation rather than reducing it [15]. In contrast, other atypical antidepressants, including bupropion, which lacks a serotonergic component to its mechanism of action [16] , agomelatine, and trazodone, being a serotonin antagonist[16] , Mitrazapine due to its unique receptor profile of blocking both histamine and serotonin[16], counterbalancing their effects, contribute to weak signals for the effect of constipation.

Serotonin–norepinephrine reuptake inhibitors (SNRIs) inhibit the reuptake of both serotonin and norepinephrine, although

their relative affinities differ. Duloxetine has a 10-fold selectivity for serotonin, meaning it is more likely to inhibit stomach motility through a sympathetic mechanism, whereas venlafaxine has a 30-fold higher affinity for serotonin than for norepinephrine. Duloxetine thus displayed a greater constipation signal [17].

Sigma-1 receptor affinity is linked to constipation as a side effect of SSRIs. In addition to the inhibiting serotonin transporter, SSRIs can interact with sigma receptors, which exist as two subtypes: sigma-1 and sigma-2. Sigma-1 receptors, which regulate motility, are abundant in the frontal cortex, hypothalamus, hippocampus, and gastrointestinal tract, particularly the submucosal layer of the stomach, duodenum, ileum, and colon. Fluvoxamine is the SSRI with the strongest affinity for the sigma-1 receptor and the highest frequency of constipation, followed by citalopram, escitalopram, sertraline, and fluoxetine. Fluvoxamine also showed the strongest signal among SSRIs in our investigation [18]. Fluvoxamine also displayed the strongest signal among SSRIs in our investigation.

Several limitations of this study should be acknowledged. First, disproportionality analyses were conducted exclusively using the FAERS database, as VigiAccess and EudraVigilance do not provide sufficient publicly available data to calculate these measures. Inclusion of full datasets from these databases could improve the robustness and generalizability of the findings. Second, prescribing patterns for antidepressants vary substantially across countries, and differences in drug availability and regulatory approval may influence reporting rates of adverse events. This affects the voluntary reporting, especially to the FAERS database, which consists primarily of data from developed countries. Last but not least, spontaneous reporting systems capture suspected adverse events without establishing causality and are subject to underreporting, reporting bias, and incomplete data, all of which may affect signal detection.

CONCLUSION

Clinicians must consider a patient's risk factors for constipation and remember that antidepressants differ in their tendency to cause constipation.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ACKNOWLEDGEMENT

We would like to express our gratitude to the digital research and writing tools that assisted during the preparation of this research work. ChatGPT (OpenAI) was used for helping locate relevant academic resources and QuillBot for paraphrasing and improving sentence structure.

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Signali za opstipaciju izazvanu antidepresivima: analiza baze spontanih prijava neželjenih događaja FDA

Milanjot Kaur, Kunal Choudhary, Slobodan M. Janković

Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Kragujevac, Srbija

KRATAK SADRŽAJ

Uvod: Dobro je poznato da 43% pacijenata sa velikim depresivnim poremećajem prestaje da uzima lekove zbog neželjenih efekata. Studije ukazuju da korisnici antidepresiva mogu imati opstipaciju. Stoga je važno proceniti bezbednost ovih lekova u odnosu na gastrointestinalni sistem, jer hronične bolesti mogu značajno uticati na kvalitet života, produktivnost rada i potencijalno povećati zdravstvene rizike.
Cilj: Cilj studije bio je da se procene potencijalni signali opstipacije povezane sa antidepresivima u javno dostupnim bazama podataka, koje sadrže spontane izveštaje o neželjenim događajima lekova.
Materijal i metode: Koristili smo javno dostupne baze podataka o spontanim izveštajima o događajima vezanim za lekove. Sistem za prijavljivanje neželjenih događaja Američke agencije za hranu i lekove (FAERS), ViggiBase, kojoj se pristupa preko VigiAccess portala, i baza podataka EudraVigilance koju je uspostavila Evropska agencija za lekove, čine osnovu ove sekundarne istraživačke studije. Za neželjeni događaj opstipacije izračunate su sledeći pokazatelji nesrazmernosti: odnos šansi za prijavljivanje (ROR), Julov Q koeficijent, odnos proporcionalnosti za prijavljivanje (PRR) i informativna komponenta (IC).
Rezultati: Među antidepresivima, najjači signali za opstipaciju u opadajućem redosledu imali su nortriptilin (ROR=8,89), nefazodon (ROR=4,21), amitriptilin (ROR=4,05), trimipramin (ROR=4,01), amoksapin (ROR=3,96), fluvoksamin (ROR=3,74) i duloksetin (ROR=3,63). Antidepresivi sa slabim signalima bili su escitalopram, fluoksetin, sertralin, agomelatin, bupropion, desvenlafaksin i milnacipran.
Zaključak: Kliničari moraju uzeti u obzir postojeće faktore rizika pacijenta za opstipaciju i biti svesni da se antidepresivi razlikuju po sklonosti da izazovu zatvor. Stoga, antidepresivi sa najmanjom verovatnoćom da izazovu zatvor, kao što su escitalopram, fluoksetin, sertralin i bupropion, treba da se propisuju u ovim situacijama.

Ključne reči: antidepresivi, opstipacija, neželjeni događaj, spontano prijavljivanje, pokazatelji nesrazmernosti

Received: **February** 17, 2026
Accepted: **March** 27, 2026