



International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
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ARTICLE TITLE INVESTIGATING LONG-TERM SIDE EFFECTS OF SNRI: VENLAFAXINE, DULOXETINE, DESVENLAFAXINE, MILNACIPRAN, AND LEVOMILNACIPRAN ANTIDEPRESSANTS TREATMENT IN PATIENTS DIAGNOSED WITH DEPRESSION

DOI [https://doi.org/10.31435/ijitss.1\(49\).2026.4659](https://doi.org/10.31435/ijitss.1(49).2026.4659)

RECEIVED 14 December 2025

ACCEPTED 23 February 2026

PUBLISHED 06 March 2026

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INVESTIGATING LONG-TERM SIDE EFFECTS OF SNRI: VENLAFAXINE, DULOXETINE, DESVENLAFAXINE, MILNACIPRAN, AND LEVOMILNACIPRAN ANTIDEPRESSANTS TREATMENT IN PATIENTS DIAGNOSED WITH DEPRESSION

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ABSTRACT

Depression is a prevalent mental health disorder affecting approximately 4% of the global population. Pharmacological management commonly involves the use of serotonin–norepinephrine reuptake inhibitors (SNRIs), including venlafaxine, duloxetine, desvenlafaxine, milnacipran, and levomilnacipran. Although these agents are effective in alleviating depressive symptoms, their prolonged use raises concerns regarding long-term safety. Clinical guidelines recommend antidepressant (AD) therapy for at least six months following symptom remission after the first episode of major depression; however, in practice, treatment duration often extends for years. Extended exposure to SNRIs has been associated with both common short-term adverse effects—such as weight gain, appetite changes, and sexual dysfunction—and less understood long-term outcomes, including metabolic, cardiovascular, and skeletal complications. The objective of this study is to systematically evaluate existing literature on the long-term side effects of SNRI therapy in patients diagnosed with depression. By synthesizing current evidence, this review aims to enhance understanding of the risk profile associated with chronic SNRI use and inform safer clinical practices.

KEYWORDS

Antidepressants, SNRI, Serotonin–Norepinephrine Reuptake Inhibitors, Selective Serotonin Reuptake Inhibitors, SSRI, Depression, Long Term Side Effects, Adverse Effects, Venlafaxine, Duloxetine, Desvenlafaxine, Milnacipran, Levomilnacipran

CITATION

Olivia Grygorcewicz, Marta Czachorowska, Franciszek Szweda, Tomasz Poczwardowski, Adrianna Kaczmarek, Katarzyna Anna Kowalska, Jakub Tomasz Latos, Marcin Chwalczuk, Marta Koneczna, Karolina Alicja Krystyniak, Kinga Augustyniak. (2026) Investigating Long-Term Side Effects of SNRI: Venlafaxine, Duloxetine, Desvenlafaxine, Milnacipran, and Levomilnacipran Antidepressants Treatment in Patients Diagnosed With Depression. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.4659

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Introduction

Depression is a widely recognized mental health condition, and most individuals are either familiar with the disorder or know someone affected by it. Despite its prevalence, misconceptions persist, with some perceiving depression as merely a sign of laziness. In reality, depression is a serious and common mood disorder that profoundly impacts not only the lives of patients, but also their families and communities. According to data from the World Health Organization, approximately 4% of the global population—equivalent to around 280 million individuals—is affected by depression at any given time (IHME, 2024; data for 2021). Diagnosis of depression requires the presence of characteristic symptoms, such as:

- persistent sadness lasting at least two weeks (without an identifiable cause),
- diminished interest or pleasure in previously enjoyable activities,
- disturbances in sleep.

Depression is one of the most prevalent civilization diseases. We can observe an increase in incidence of major depressive disease in the last few decades. Moreover, there are innumerable scientific studies showing comorbidity of major depressive disease with chronic somatic disorders. Biffi et al. (2018), found that the impact of major depressive disorder (MDD) is particularly significant in cardiology, as clinical guidelines in this field recommend the use of antidepressant therapy as one of several strategies to reduce mortality. Effective management of depression in patients with cardiovascular disease has been associated with improved treatment adherence and increased patient longevity.

Pharmacological treatment typically involves the use of first-line antidepressant medications, primarily selective serotonin reuptake inhibitors (SSRIs), as they are used as gold standard for treating depression, nevertheless serotonin–norepinephrine reuptake inhibitors (SNRIs) are prescribed with a frequency comparable to that of SSRIs in the treatment of depression (Pająk et al., 2021). This group of pharmaceutical drugs consists of: venlafaxine, duloxetine, desvenlafaxine, and levomilnacipran. This article will focus and further explore the adverse effects of long time usage of these pharmaceuticals.

SNRIs represent a versatile class of pharmacological agents with therapeutic applications extending well beyond major depressive disorder. These medications are known for their broader impact on the human organism, for example: coanalgesic effect in peripheral neuropathic pain. These medications are prescribed not only for major depressive disorder, but also for a range of other psychiatric conditions, including: obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, post-traumatic stress disorder, and bulimia nervosa (Montgomery & Thase, 2000). Moreover, SNRIs are used also in fibromyalgia and mentioned above chronic neuropathic pains. Consequently, the number of individuals using SSRIs and SNRIs exceeds the number of people diagnosed solely with depression. Given the increasing prevalence of depressive and anxiety-related disorders, it is unsurprising that the use of SSRIs and SNRIs continues to rise globally. A study conducted in the United States reported that 13.2% of adults had used antidepressant medications within the previous 30 days (Brody & Gu, 2020). Similarly, *Heald et al. (2020)* data from the United Kingdom indicate that the total number of antidepressant doses taken by patients has doubled over a ten-year period.

Current clinical guidelines recommend the use of ADs for at least 6 months following the remission of depressive symptoms (Montgomery & Thase, 2000). In practice, however, the continuation phase of treatment often extends far beyond this period. This is understandable, as discontinuation decisions must carefully balance the risk of relapse against the potential benefits of ongoing therapy. Dekker, et al., (2000) reported that the primary reasons patients remain on this treatment include fear of withdrawal symptoms and concern about symptom recurrence. Evidence suggests that both patients and physicians tend to prolong AD use. While prescribing guidelines clearly state that treatment should continue for at least six months, they often lack specific recommendations regarding the maximum duration of pharmacotherapy, largely due to individual variability in treatment response. Nevertheless, previous studies indicate that patients who used antidepressants for more than three years reported more severe side effects compared to those treated for less than two years (*Hansen & Gaynes, 2014*). Concerns have also been raised about the lesser-known consequences of long-term antidepressant use compared to short-term treatment. Commonly reported early side effects include weight gain, changes in appetite, and sexual or sleep disturbances. However, the adverse effects of prolonged antidepressant therapy remain insufficiently understood. One of the few studies focused on continuous antidepressant use beyond three years (Cartwright, 2016) found that some patients expressed a need for more information regarding long-term risks, as well as greater support for medication discontinuation. Furthermore, findings from Andersohn et al. (2009) identified several potential long-term risks associated with antidepressant therapy, including:

- increased incidence of osteoporosis and bone fractures,
- bleeding disorders,
- hyponatremia,
- and diabetes mellitus.

These observations highlight the wide-ranging physiological impacts of ADs, which may vary depending on the duration of use. In light of these considerations. It is essential to review the epidemiology and mechanisms of long-term adverse effects associated with pharmacological treatment of depression. Such an analysis would provide clinicians and researchers with a comprehensive understanding of the risks and benefits of extended ADs use. Therefore, the aim of the present study is to evaluate existing literature and synthesize current findings regarding the long-term consequences of continuous SNRI treatment.

Mechanisms of Action and Pharmacokinetics of SNRIs

Inhibition of both serotonin transporter (SERT) and noradrenaline transporter (NAT) allow higher concentration of both serotonin and norepinephrine in synaptic cleft, giving a wider range of both therapeutic advantages and possible side effects. Higher serotonin level in brain cells improves mood and reduces anxiety, whereas higher norepinephrine levels improve energy, alertness, and pain modulation.

Most SNRIs are well absorbed, metabolised in the liver, mostly by the protein CYP2D6. Despite the metabolisation process taking place in the liver, in the vast majority SNRIs are primarily excreted in urine. Up to 90% of the total dose may be eliminated via this pathway. Although pharmacokinetic interactions among SNRIs are relatively uncommon, it is important to underscore the potential risk of a lowered seizure threshold. Consequently, when agents known to reduce the seizure threshold—such as bupropion, which is frequently co-administered with SNRIs for overlapping clinical indications—are prescribed, dose reductions and heightened clinical vigilance are advised.

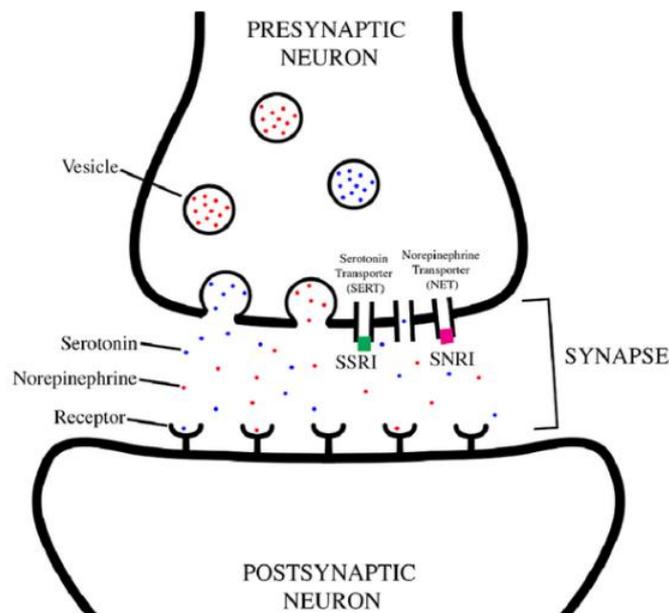


Fig. 1.
(Foster & Smith, 2023,).

Methodology

The methodology of this research consists of a review of data available in PubMed from 2000 to the present times. This research employs a review-article methodology, focusing on the analysis of long-term adverse effects (over 8 weeks) in order to identify potential correlations and recurrent symptom patterns in SNRI treatment.

Venlafaxine

Venlafaxine is an antidepressant used not only in major depressive disorder, but has important off label usage. Due to uptake of norepinephrine in synaptic cleft it has stimulating properties and it helps in neurological symptoms like chronic neuropathic pain. Every drug has its limitation, most of them coming from side effects. Venlafaxine is metabolised in liver, by CYP2D6, but is excreted by urine. Most common side effects are nausea, loss of appetite, constipation, dry mouth, dizziness, sweating, insomnia. It is important to be especially cautious when a patient presents suicidal tendencies as it may increase the probability of attempting suicide. Less common side effects occurring in less than 1 per 100 patients using venlafaxine are weight gain or loss, low sodium levels. Long term side effects are not observed besides non-clinically important rise in sexual dysfunction. Studies show no important correlation between venlafaxine and miscarriages or malformations. Brain zaps are observed both in long term therapy and more often when patients reduce or miss doses of venlafaxine.

Duloxetine

Duloxetine became available for patients with massive depression disorders in the early 2000s. Despite being a first line antidepressant medicine, it is also used for treatment of neuropathic pain, fibromyalgia, chronic musculoskeletal pain and chemotherapy-induced peripheral neuropathy. It operates by increasing serotonin and norepinephrine levels in the brain and spinal cord. Additional action includes mild inhibition of dopamine reuptake in the prefrontal cortex, which contributes slightly to motivation and focus. According to Parahia et al. (2006) common side effects include nausea, dry mouth, headache, dizziness, insomnia or sleepiness, constipation, and sweating, most of which are usually mild and improve over time. A recent case report by Scorza CA et al. (2024) describes a single 80 year old patient, who developed daytime bruxism, tardive orofacial dyskinesia and dysphagia after 9 years of duloxetine uptake. Research suggests it could be due to the serotonin-dopamine imbalance. However, this study was not conducted on a greater group of patients, so further conclusions regarding a population cannot be established. It is generally well tolerated and helpful for patients who have both mood symptoms and pain.

Desvenlafaxine

Desvenlafaxine, a serotonin–norepinephrine reuptake inhibitor (SNRI) widely used for major depressive disorder, has a safety and tolerability profile consistent with its drug class, but long-term use has been associated with a number of potential adverse effects. Integrated analyses of clinical trials have documented treatment-emergent side effects such as changes in blood pressure and sexual dysfunction, which may persist with continued therapy and affect adherence. Long-term administration can also result in withdrawal symptoms upon discontinuation, indicating the need for gradual tapering when treatment is modified. Additionally, adverse reactions including nausea, headache, dizziness, and irritability may emerge or persist over extended treatment periods, underscoring the importance of ongoing monitoring in patients receiving desvenlafaxine (Coupland et al., 2011; Liebowitz et al., 2009; *Discontinuation Symptoms Study*, 2009).

Levo Milnacipran

Milnacipran being selective serotonin and norepinephrine reuptake inhibitor is used, as most drugs from this group, in treatment of major depression disorder among other both somatic and mental illnesses. Most commonly occurring adverse events are gastrointestinal ones, e.g. nausea, dry mouth, constipation, oral hypoesthesia. Recent studies suggest middle aged and elderly patients are more receptive to those side effects. Among typical side effects, it's important to highlight the risk of hyponatremia in elderly, especially when they are also treated with diuretic medicines.

Summary and conclusions

Serotonin–norepinephrine reuptake inhibitors (SNRIs) remain widely prescribed for major depressive disorder and a growing range of psychiatric and somatic conditions; however, their extended use is increasingly associated with a spectrum of long-term adverse effects that warrant careful clinical consideration. Evidence indicates that prolonged antidepressant therapy, including SNRIs, significantly increases the risk of hyponatremia, particularly in vulnerable populations, underscoring the need for regular electrolyte monitoring during long-term treatment (*Li et al.*, 2025). Additionally, long-term serotonergic antidepressant use has been linked to increased fracture risk, suggesting potential impacts on bone health that may exacerbate osteoporotic complications, especially in older adults (*Cheung et al.*, 2014). Emerging cohort data also demonstrate associations between chronic antidepressant exposure and metabolic and cardiovascular outcomes, including elevated risks of coronary heart disease and mortality over extended follow-up periods (*Di-an et al.*, 2023). Collectively, these findings highlight the importance of individualized risk–benefit assessment, patient education, and ongoing monitoring when considering prolonged SNRI therapy. Further prospective research is necessary to clarify causal mechanisms and inform optimized long-term treatment strategies.

Disclosures

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All authors have read and agreed to the published version of the manuscript.

Funding Statement: The author received no external funding for this work.

Institutional Review Board Statement: Not applicable; this review included only published data.

Informed Consent Statement: Not applicable.

Data Availability Statement: All supporting data are available within the cited peer-reviewed literature.

Acknowledgments: The author acknowledges the contribution of investigators and data curators whose high-quality research underpins the advances reviewed herein.

Conflict of Interest Statement: The author declares no conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process. In preparing this work, the authors used ChatGPT for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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Abbreviation	Full Term
MDD	Major Depressive Disorder
SNRI	Serotonin–Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
AD	Antidepressant
SERT	Serotonin Transporter
NAT	Noradrenaline Transporter
WHO	World Health Organization
CYP2D6	Cytochrome P450 2D6 (liver enzyme)