

Kulynych H.B., Ersteniuk H.M., Klishch I.P., Herashchenko S.B., Oliynyk R.P., Merena S.R.
Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

EFFECT OF VORTIOXETINE ON THE PROOXIDANT-ANTIOXIDANT BALANCE IN EXPERIMENTAL NEUROTOXICITY INDUCED BY CISPLATIN AND PACLITAXEL

e-mail: galija1979@ukr.net

Chemotherapy-induced neurotoxicity is a common complication of paclitaxel and cisplatin treatment and is associated with disruption of the prooxidant-antioxidant balance. The purpose of the study was to evaluate the effects of prophylactic and therapeutic administration of vortioxetine on indicators of the prooxidant-antioxidant balance in experimental neurotoxicity. The study was performed in sexually mature male white inbred rats. Vortioxetine was administered at a dose of 5 mg/kg/day using either a prophylactic or a therapeutic regimen. Plasma levels of thiobarbituric acid-reactive substances, superoxide dismutase activity, and reduced glutathione content were determined on days 14, 28, 60, 90, and 120. Administration of the cytostatic agents resulted in the most pronounced disturbance of the prooxidant-antioxidant balance on days 14–28. Vortioxetine attenuated oxidative disturbances in both neurotoxicity models, while the prophylactic regimen was associated with better preservation of antioxidant defense parameters. These findings indicate that vortioxetine mitigates oxidative stress associated with chemotherapy-induced neurotoxicity.

Keywords: vortioxetine, paclitaxel, cisplatin, chemotherapy-induced neurotoxicity, oxidative stress, prooxidant-antioxidant balance, superoxide dismutase, reduced glutathione, thiobarbituric acid-reactive products.

Кулинич Г.Б., Ерстенюк Г. М., Кліш І.П., Геращенко С.Б., Олійник Р.П., Мерена С.Р.

ВПЛИВ ВОРТІОКСЕТИНУ НА ПРООКСИДАНТНО-АНТИОКСИДАНТНИЙ БАЛАНС ПРИ ЕКСПЕРИМЕНТАЛЬНІЙ НЕЙРОТОКСИЧНОСТІ, ІНДУКОВАНІЙ ЦИСПЛАТИНОМ І ПАКЛІТАКСЕЛОМ

Хіміотерапевтично індукована нейротоксичність є поширеним ускладненням застосування паклітакселу та цисплатину, розвиток якого пов'язаний із порушенням прооксидантно-антиоксидантної рівноваги. Метою дослідження було оцінити вплив профілактичного та лікувального застосування вортіоксетину на показники прооксидантно-антиоксидантного балансу за експериментальної нейротоксичності. Дослідження виконано на статевозрілих самцях білих інбредних щурів. Вортіоксетин застосовували у дозі 5 мг/кг/добу профілактично або лікувально. На 14, 28, 60, 90 та 120-ту добу визначали рівень тіобарбітуровоокисотно-активних продуктів, активність супероксиддисмутази та вміст відновленого глутатіону. Введення цитостатиків супроводжувалося найбільш вираженим порушенням прооксидантно-антиоксидантного балансу на 14–28-му добу. Застосування вортіоксетину зменшувало вираженість оксидативних порушень в обох моделях, а профілактичний режим забезпечував більш виражене збереження показників антиоксидантного захисту. Отримані результати свідчать про здатність вортіоксетину послаблювати прояви оксидативного стресу, спричиненого хіміотерапевтично індукованою нейротоксичністю.

Ключові слова: вортіоксетин, паклітаксел, цисплатин, хіміотерапевтично індукована нейротоксичність, оксидативний стрес, прооксидантно-антиоксидантний баланс, супероксиддисмутаза, відновлений глутатіон, продукти, що реагують з тіобарбітуровою кислотою.

The study is a fragment of the research project "Pathophysiological and Morphofunctional Changes in Organs and Body Systems under the Influence of Antitumor Drugs and Methods for Their Correction", state registration No. 0125U004275.

Cisplatin and paclitaxel are widely used in anticancer therapy; however, their use may be associated with chemotherapy-induced peripheral neuropathy, which manifests as sensory, painful, and motor disturbances and may persist after treatment completion. Its pathogenesis is multifactorial and involves impaired axonal transport, mitochondrial dysfunction, oxidative stress, neuroinflammation, and alterations in neuronal signaling systems [7, 11].

Paclitaxel-induced neurotoxicity is associated with disruption of the neuronal microtubule apparatus, leading to impaired axonal transport and dysfunction of peripheral nerve fibers [13]. Mitochondrial dysfunction, excessive generation of reactive oxygen species, and depletion of antioxidant defenses also contribute to its development. Duggett et al. demonstrated that reactive oxygen species production and antioxidant enzyme activity vary according to the stage of

development and resolution of paclitaxel-induced neuropathy, indicating a temporal component of redox disturbances [5].

Oxidative stress is also regarded as a major pathogenic mechanism underlying cisplatin-induced neurotoxicity. Mitochondrial dysfunction, excessive reactive oxygen species generation, enhanced lipid peroxidation, and depletion of endogenous antioxidant reserves contribute to nervous tissue injury [4]. Experimental evidence confirms the involvement of oxidative stress and impaired antioxidant defense in cisplatin-induced neurotoxicity [1].

Given the importance of redox disturbances in cytostatic-induced neurotoxicity, the search for agents capable of modulating associated neurochemical and cellular processes remains relevant. Vortioxetine, a multimodal serotonergic agent whose effects extend beyond modulation of serotonergic neurotransmission, is of particular interest. Experimental models have demonstrated its

effects on neuroinflammatory processes and oxidative stress-related alterations [12]. Akyuz Cim et al. reported changes in biochemical and histopathological markers in a rat model of stress-induced brain injury following vortioxetine administration [2]. However, findings from other models of nervous tissue injury cannot be directly extrapolated to cytostatic-induced neurotoxicity.

In our previous study, vortioxetine affected the neurophysiological manifestations of chemotherapy-induced peripheral neuropathy in rats [6]. However, it remains insufficiently understood whether vortioxetine administration affects the systemic prooxidant–antioxidant balance, how these changes evolve over time, and whether they depend on the timing of intervention. Comparison of prophylactic and therapeutic regimens may clarify the effects of vortioxetine on the development and subsequent dynamics of redox disturbances.

The purpose of the study was to determine the effects of prophylactic and therapeutic administration of vortioxetine on the temporal dynamics of blood plasma prooxidant–antioxidant balance indicators in experimental neurotoxicity induced by cisplatin and paclitaxel.

Materials and methods. The study was conducted in sexually mature male white inbred rats weighing 180–220 g. The use of one sex ensured sex-related homogeneity of the experimental groups and excluded sex as an additional biological source of variability in the investigated parameters. However, the exclusive use of males precluded assessment of potential sex-related differences in cytostatic-induced redox disturbances and responses to the investigated pharmacological intervention; this limitation should be considered when interpreting and extrapolating the findings.

The animals were housed in the vivarium of Ivano-Frankivsk National Medical University under controlled conditions at 22 ± 2 °C, 55–60 % relative humidity, and a 12-h light/dark cycle, with free access to drinking water and standard laboratory chow. Five animals were housed per cage with a plastic base and metal grid measuring 40×30×20 cm. Sawdust was used as bedding, and gnawing materials were provided for environmental enrichment. Bedding replacement, cage cleaning, and other husbandry procedures followed the standard sanitary and hygienic procedures of the animal facility. Before the experiment, the animals underwent a 7-day acclimatization period.

The study was conducted from April to October 2025. All experimental procedures complied with the requirements for the ethical use and care of laboratory animals. The protocol was approved by the Ethics Committee of Ivano-Frankivsk National Medical University (Protocol No. 146/24 dated September 26, 2024).

Experimental design. Seven experimental groups of 30 animals each were formed: control; paclitaxel; cisplatin; paclitaxel plus prophylactic vortioxetine; paclitaxel plus therapeutic vortioxetine; cisplatin plus prophylactic vortioxetine; and cisplatin plus therapeutic vortioxetine.

Control animals were not exposed to cytostatic agents and received intraperitoneal injections of 0.9 % sodium chloride solution at the corresponding time points. Paclitaxel (Actavis, Romania/Iceland) was administered intraperitoneally at 2 mg/kg every other day for four injections, with a cumulative dose of 8 mg/kg. Paclitaxel-induced neurotoxicity was modeled according to the experimental approach described by Polomano et al. [9]. Cisplatin (Pfizer, USA) was administered intraperitoneally at 2 mg/kg twice weekly for 4 weeks, with a cumulative dose of 16 mg/kg. The cisplatin dose and administration frequency were selected with reference to an experimental model of cisplatin-induced neurotoxicity [14], and the duration of cytostatic exposure was adapted to the present study design.

In the four combined-treatment groups, vortioxetine (Brintellix, H. Lundbeck A/S, Denmark) was administered intragastrically at 5 mg/kg once daily during the corresponding paclitaxel or cisplatin regimen. Prophylactic treatment began 5 days before the first paclitaxel or cisplatin injection, whereas therapeutic treatment began on day 3 after initiation of cytostatic exposure in the respective neurotoxicity model. The vortioxetine dose was selected based on our previously tested experimental approach to its use in chemotherapy-induced peripheral neuropathy in rats [6]. The prophylactic and therapeutic regimens were established to compare drug effects according to the timing of pharmacological intervention.

In the control, paclitaxel, and cisplatin groups, biological material was collected on days 1, 7, 14, 28, 60, 90, and 120. Animals were distributed across these seven observation time points, with 4–5 animals assigned to each time point and 30 animals in each group. In the prophylactic and therapeutic vortioxetine groups, biological material for biochemical analysis was collected on days 14, 28, 60, 90, and 120, with six animals assigned to each time point and 30 animals in each group. Comparative biochemical analysis included days 14, 28, 60, 90, and 120 because these time points were common to the cytostatic-exposure and vortioxetine groups.

The cytostatic-exposure regimens were developed with reference to experimental models of paclitaxel- and cisplatin-induced neurotoxicity [9, 14]. Interspecies dose conversion based on body surface area was performed according to Reagan-Shaw et al. [10], using K_m factors of 6 for rats and 37 for humans. The calculated values were used to characterize interspecies exposure and justify the approximate magnitude of the administered doses, rather than as evidence of direct clinical equivalence of the experimental regimens.

Biochemical analyses. Blood samples were collected into heparinized tubes, followed by plasma separation. The prooxidant–antioxidant system was assessed spectrophotometrically by measuring plasma TBA-active products (TBA-AP) as an indicator of lipid peroxidation intensity and superoxide dismutase (SOD) activity and reduced glutathione (GSH) concentration as indicators of antioxidant defense.

Total protein concentration in blood plasma was determined by the method described by Lowry et al. The measured values were used to normalize the biochemical parameters and express them per milligram of protein.

Plasma TBA-AP was determined by reaction with 2-thiobarbituric acid according to the Wills method, which is based on the formation of a colored complex between lipid peroxidation products and thiobarbituric acid. The reaction mixture was heated in a boiling water bath for 60 min, rapidly cooled, and centrifuged. Supernatant absorbance was measured spectrophotometrically at 532 nm against a reagent blank. Results were normalized to total protein content and expressed as nmol TBA-AP/mg protein.

SOD activity was determined by the Marklund and Marklund method based on the ability of the enzyme to inhibit pyrogallol autoxidation in an alkaline medium. The reaction was performed at 25 °C in a buffer at pH 8.2, and absorbance changes were recorded at 420 nm. One unit of SOD activity was defined as the amount of enzyme required to inhibit the rate of pyrogallol autoxidation by 50 %. Values were normalized to total protein concentration and expressed as arbitrary units/mg protein.

GSH concentration was determined by the Ellman method based on the reaction of the sulfhydryl groups of reduced glutathione with 5,5'-dithiobis-(2-nitrobenzoic acid), resulting in the formation of a colored product. Absorbance was measured spectrophotometrically at 412 nm against a control sample. GSH concentration was calculated from a calibration curve, normalized to total protein content, and expressed as $\mu\text{mol/mg}$ protein.

All biochemical measurements were performed in three technical replicates. For each biological sample, the mean of the three measurements was calculated and used in the subsequent statistical analysis. Technical replicates were not treated as independent observations.

Statistical analysis. The individual animal was considered the statistical unit. The number of animals at each time point was 4–5 in the control, paclitaxel, and cisplatin groups and six in the prophylactic and therapeutic vortioxetine groups. Normality of quantitative variables was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated using Levene's test. Between-group differences were analyzed separately at each observation time point. When the assumptions for parametric analysis were met, one-way analysis of variance (one-way ANOVA) followed by Tukey's post hoc test for multiple pairwise comparisons was applied. The control group was compared with the corresponding cytostatic-exposure group; each cytostatic group was compared with the prophylactic and therapeutic vortioxetine groups; and the prophylactic and therapeutic regimens were compared with each other. Results were presented as mean $\pm$ standard deviation ($M \pm SD$). Differences were considered statistically significant at $p < 0.05$.

Results of the study. Evaluation of the prooxidant-antioxidant system revealed pronounced

time-dependent changes in oxidative stress markers in both paclitaxel- and cisplatin-induced neurotoxicity. The greatest alterations in plasma TBA-AP, SOD activity and GSH levels were observed predominantly on days 14–28 of the experiment. Vortioxetine administration attenuated these changes, with the most pronounced effects observed under the prophylactic treatment regimen.

Dynamics of plasma TBA-active products. Following paclitaxel administration, plasma TBA-AP levels increased progressively. On day 14, the level was 4.68 ± 0.25 nmol/mg protein versus 3.16 ± 0.16 nmol/mg protein in the control group ($p < 0.05$), corresponding to a 48.1 % increase. It peaked on day 28 at 5.12 ± 0.28 nmol/mg protein, 62.5 % above the control value ($p < 0.05$).

On day 14, prophylactic vortioxetine significantly reduced TBA-AP levels by 18.4 % relative to paclitaxel alone ($p < 0.05$), whereas therapeutic administration produced a 13.5 % reduction. On day 28, the corresponding reductions were 22.3 % and 17.6 %. Thereafter, TBA-AP levels gradually declined in all groups, and by day 120, values in both vortioxetine groups approached control levels.

The increase in TBA-AP following cisplatin administration developed earlier and was more pronounced than after paclitaxel. On day 14, the level reached 5.84 ± 0.31 nmol/mg protein versus 3.16 ± 0.16 nmol/mg protein in the control group ($p < 0.05$), representing an approximately 1.85-fold increase. Prophylactic and therapeutic vortioxetine reduced TBA-AP levels by 25.5 % and 19.3 %, respectively, relative to cisplatin alone. On day 28, TBA-AP remained elevated in the cisplatin group, whereas both vortioxetine regimens continued to attenuate lipid peroxidation. Levels subsequently declined, approaching control values in both vortioxetine groups by day 120. Overall, vortioxetine was associated with lower plasma TBA-AP levels than cytostatic treatment alone in both models. The effect was greatest during maximal oxidative imbalance, particularly with prophylactic administration. Quantitative temporal changes in plasma TBA-AP levels are presented in (Table 1).

Dynamics of superoxide dismutase activity. Changes in SOD activity showed a pattern opposite to that observed for plasma TBA-AP. Following administration of both cytostatic agents, SOD activity decreased, with the most pronounced suppression occurring on days 14–28. There after, enzyme activity gradually recovered, approaching the values observed in the control group.

In the paclitaxel group, SOD activity decreased to 38.2 ± 1.9 U/mg protein on day 14. Prophylactic vortioxetine administration increased SOD activity by 13.9 % compared with the paclitaxel group ($p < 0.05$), whereas therapeutic administration resulted in a 7.3 % increase. The lowest SOD activity was recorded on day 28 (34.5 ± 1.8 U/mg protein). At this time point, prophylactic vortioxetine increased SOD activity by 24.1 %, while therapeutic administration produced a 13.3 % increase compared with the paclitaxel group. Thereafter, SOD activity gradually

increased in all experimental groups, and by day 120 the differences between the vortioxetine-treated

groups and the paclitaxel group had markedly diminished.

Table 1

Dynamics of TBA-active product levels in the blood plasma of experimental animals, M $\pm$ SD, nmol/mg protein

Group	Day 14	Day 28	Day 60	Day 90	Day 120
Control	3.16 $\pm$ 0.16	3.15 $\pm$ 0.18	3.17 $\pm$ 0.15	3.16 $\pm$ 0.14	3.18 $\pm$ 0.16
Paclitaxel	4.68 $\pm$ 0.25*	5.12 $\pm$ 0.28*	4.25 $\pm$ 0.21*	3.65 $\pm$ 0.19*	3.32 $\pm$ 0.18
Paclitaxel + prophylactic vortioxetine	3.82 $\pm$ 0.21#	3.98 $\pm$ 0.20#	3.51 $\pm$ 0.18#	3.28 $\pm$ 0.15#	3.20 $\pm$ 0.16
Paclitaxel + therapeutic vortioxetine	4.05 $\pm$ 0.22#	4.22 $\pm$ 0.23#	3.70 $\pm$ 0.19#	3.38 $\pm$ 0.17	3.22 $\pm$ 0.15
Cisplatin	5.84 $\pm$ 0.31*	5.40 $\pm$ 0.29*	4.38 $\pm$ 0.23*	3.78 $\pm$ 0.20*	3.41 $\pm$ 0.17
Cisplatin + prophylactic vortioxetine	4.35 $\pm$ 0.24#	4.12 $\pm$ 0.22#	3.62 $\pm$ 0.19#	3.31 $\pm$ 0.16#	3.21 $\pm$ 0.15
Cisplatin + therapeutic vortioxetine	4.71 $\pm$ 0.26#	4.45 $\pm$ 0.24#	3.80 $\pm$ 0.20#	3.42 $\pm$ 0.17#	3.25 $\pm$ 0.16

Notes: * $p < 0.05$ vs. the control group; # $p < 0.05$ vs. the corresponding cytostatic-treated group.

A more pronounced reduction in SOD activity was observed in the cisplatin group. On day 14, SOD activity decreased to 30.5 $\pm$ 1.6 U/mg protein. Prophylactic vortioxetine administration increased SOD activity by 26.6 % compared with the cisplatin group ($p < 0.05$), whereas therapeutic administration increased it by 15.4 %. The minimum SOD activity was observed on day 28 (29.8 $\pm$ 1.6 U/mg protein). At this time point, prophylactic vortioxetine increased SOD activity by 32.2 %, while therapeutic administration resulted in a 20.1 % increase compared with the cisplatin group. Subsequently, SOD activity progressively recovered in all groups, and by day 120 the differences between the treatment groups had become minimal.

Overall, vortioxetine administration was associated with higher plasma SOD activity than that observed in the corresponding cytostatic-treated groups. The beneficial effect was most evident during the period of maximal suppression of antioxidant enzyme activity and was generally more pronounced under the prophylactic treatment regimen. The temporal changes in SOD activity according to the vortioxetine treatment regimen are shown in Fig. 1.

Dynamics of reduced glutathione content. Changes in GSH content paralleled SOD activity and were inversely related to plasma TBA-AP levels. The greatest reductions occurred on days 14–28 and were more pronounced after cisplatin than paclitaxel administration. Subsequently, GSH levels gradually approached control values.

In the paclitaxel group, GSH content on day 14 was 4.85 $\pm$ 0.23 μ mol/mg protein, compared with 5.68 $\pm$ 0.26 and 5.32 $\pm$ 0.25 μ mol/mg protein under prophylactic and therapeutic vortioxetine administration, respectively. On day 28, it decreased to 4.12 $\pm$ 0.21 μ mol/mg protein versus 6.35 $\pm$ 0.28 μ mol/mg protein in the control group ($p < 0.05$), representing a 35.1 % reduction. The corresponding values under prophylactic and therapeutic vortioxetine administration were 5.52 $\pm$ 0.24 and 5.08 $\pm$ 0.22 μ mol/mg protein, exceeding the paclitaxel value by 34.0 % and 23.3 %, respectively. GSH content increased in all three groups on days 60 and 90 but remained higher under both vortioxetine regimens than with paclitaxel alone. By day 120, the values were 5.98 $\pm$ 0.27, 6.28 $\pm$ 0.26, and 6.15 $\pm$ 0.25 μ mol/mg protein in the paclitaxel, prophylactic, and therapeutic groups, respectively.

In the cisplatin model, GSH content on day 14 was 3.45 $\pm$ 0.18 μ mol/mg protein. Prophylactic and therapeutic vortioxetine increased it to 4.82 $\pm$ 0.22 and 4.30 $\pm$ 0.20 μ mol/mg protein, corresponding to increases of 39.7 % and 24.6 %, respectively, relative to cisplatin alone. On day 28, the cisplatin value was 3.38 $\pm$ 0.17 μ mol/mg protein, whereas prophylactic and therapeutic vortioxetine increased it to 4.95 $\pm$ 0.23 and 4.41 $\pm$ 0.21 μ mol/mg protein, respectively, representing increases of 46.4 % and 30.5 %. GSH content gradually increased in all groups on days 60 and 90 but remained higher under both vortioxetine regimens than with cisplatin alone. By day 120, the corresponding values were 5.72 $\pm$ 0.26, 6.18 $\pm$ 0.25, and 5.98 $\pm$ 0.24 μ mol/mg protein.

Thus, vortioxetine administration was associated with higher GSH levels than cytostatic treatment alone, although between-group differences diminished at later time points. The temporal changes in GSH content are presented in Fig. 2.

Integrated assessment of the prooxidant–antioxidant balance. The three parameters showed a consistent pattern: plasma TBA-AP accumulation was accompanied by decreased SOD activity and GSH content. The greatest deviations occurred on days 14–28; in the cisplatin model, they developed earlier and were more pronounced.

In the paclitaxel model, the largest between-group differences were observed on day 28. Compared with paclitaxel alone, prophylactic vortioxetine was associated with 22.3 % lower plasma TBA-AP, 24.1 % higher SOD activity, and 34.0 % higher GSH content.

In the cisplatin model, differences were evident by day 14, when prophylactic vortioxetine was associated with 25.5 % lower TBA-AP and 26.6 % and 39.7 % higher SOD activity and GSH content, respectively. On day 28, the corresponding increases in SOD activity and GSH content reached 32.2 % and 46.4 %.

At later time points, between-group differences gradually diminished as the systemic prooxidant–antioxidant balance recovered. Overall, vortioxetine was associated with less pronounced marker alterations than cytostatic treatment alone.

Discussion. The obtained results indicate that both paclitaxel- and cisplatin-induced neurotoxicity were associated with a time-dependent imbalance between lipid peroxidation and antioxidant defense. The most pronounced changes were observed on days 14–28, with

increased plasma TBA-AP levels accompanied by decreased SOD activity and GSH content. Vortioxetine administration was associated with less pronounced alterations in these parameters than those observed in the corresponding cytostatic-treated groups.

These findings are consistent with the established role of oxidative stress in chemotherapy-induced

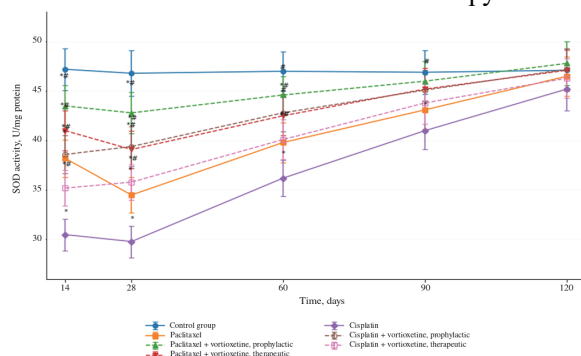


Fig. 1. Dynamics of superoxide dismutase activity in the blood plasma of experimental animals under prophylactic and therapeutic administration of vortioxetine, $M \pm SD$. Notes: * $p < 0.05$ compared with the control group; # $p < 0.05$ compared with the corresponding cytostatic group

In paclitaxel-induced neuropathy, oxidative stress changes dynamically during the development and resolution of neuropathy [5]. In the present study, the most pronounced changes in TBA-AP, SOD activity, and GSH content in the paclitaxel group occurred on day 28, followed by partial recovery. This temporal pattern is consistent with the multifactorial pathogenesis of paclitaxel-induced peripheral neuropathy, which involves impaired microtubule dynamics and axonal transport, mitochondrial dysfunction, oxidative stress, and neuroinflammatory mechanisms [13]. Vortioxetine was associated with lower lipid peroxidation and better preservation of antioxidant defense, particularly on day 28, suggesting attenuation rather than complete prevention of the redox imbalance.

In the cisplatin model, impairment of antioxidant defense was evident earlier, particularly on day 14. This may reflect the prominent contribution of mitochondrial damage, reactive oxygen species generation, lipid peroxidation, and impaired endogenous antioxidant defense to cisplatin neurotoxicity [1, 4, 8]. Serotonergic neurotransmission may also contribute to cisplatin-induced neurotoxicity [15]. A recent review further supports the interconnected roles of oxidative, mitochondrial, and inflammatory mechanisms in this model [4].

Vortioxetine similarly attenuated the impairment of antioxidant defense in cisplatin-induced neurotoxicity, with the greatest differences between the vortioxetine-treated and cisplatin groups observed during days 14–28. Across both models, lower TBA-AP levels were accompanied by higher SOD activity and GSH content in animals receiving vortioxetine, indicating a less pronounced systemic redox imbalance. However, these findings do not establish a direct antioxidant effect of vortioxetine because direct reactive oxygen species scavenging and specific molecular targets within the antioxidant defense system were not investigated.

peripheral neuropathy. Mitochondrial dysfunction and excessive reactive oxygen species generation contribute to oxidative damage and represent important mechanisms underlying chemotherapy-induced peripheral neuropathy [3]. Thus, the concurrent increase in TBA-AP and decrease in SOD activity and GSH content indicate a shift toward a prooxidant state.

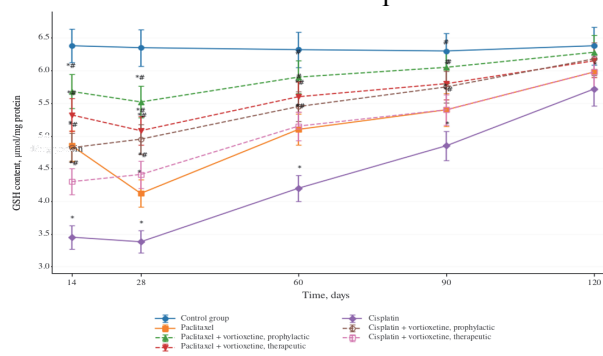


Fig. 2. Dynamics of reduced glutathione content in the blood plasma of experimental animals, $M \pm SD$. Notes: * $p < 0.05$ compared with the control group; # $p < 0.05$ compared with the corresponding cytostatic group.

Experimental studies suggest that vortioxetine may influence oxidative and neuroinflammatory processes. In a rotenone-induced model of Parkinsonism, vortioxetine attenuated neuroinflammatory changes and improved functional outcomes [12], while another study reported changes in biochemical and histopathological parameters in a rat model of stress-induced brain injury following vortioxetine administration [2]. However, differences between these models and cytostatic-induced neurotoxicity limit direct extrapolation of these mechanisms to the present findings.

The biochemical results are also consistent with our previous study showing that vortioxetine affected neurophysiological manifestations of chemotherapy-induced peripheral neuropathy in rats [6]. Together, the functional and biochemical findings provide a broader characterization of vortioxetine effects, although they do not establish a direct causal relationship between plasma redox biomarkers and peripheral nerve recovery.

The prophylactic regimen showed numerically more favorable TBA-AP, SOD, and GSH values than the therapeutic regimen during days 14–28 in both models. However, because these differences were not supported by separately confirmed statistically significant post hoc comparisons, they should be considered a descriptive trend rather than evidence supporting the superiority of the prophylactic regimen. The therapeutic regimen was also associated with less pronounced redox disturbances than the corresponding cytostatic-treated groups, despite being initiated after cytostatic exposure. These experimental findings cannot be directly extrapolated to clinical efficacy.

At later time points, between-group differences gradually diminished, mainly because of partial recovery of the investigated parameters in the cytostatic-treated groups. Therefore, the smaller differences observed on days 90–120 should not

necessarily be interpreted as indicating the disappearance of vortioxetine effects.

Limitations. This study assessed systemic prooxidant–antioxidant balance using plasma levels of TBA-active products, superoxide dismutase activity, and reduced glutathione content. Therefore, it cannot directly characterize redox disturbances in peripheral nervous tissue or

clarify the molecular mechanisms underlying the effects of vortioxetine. Mitochondrial dysfunction, neuroinflammation, and redox-sensitive signaling pathways were not evaluated and warrant further investigation. As these findings derive from a rat model of neurotoxicity, they should not be directly extrapolated to the clinical efficacy of vortioxetine in patients.

Conclusions

1. Paclitaxel- and cisplatin-induced neurotoxicity was associated with a time-dependent disturbance of the systemic prooxidant–antioxidant balance, characterized by increased plasma TBA-active product levels accompanied by decreased superoxide dismutase activity and reduced glutathione content. The most pronounced alterations were observed on days 14–28 of the experiment.

2. Prophylactic administration of vortioxetine at a dose of 5 mg/kg/day was associated with less pronounced redox disturbances in both neurotoxicity models. On day 28 of the paclitaxel-induced neurotoxicity model, plasma TBA-AP levels were 22.3 % lower, whereas SOD activity and GSH content were 24.1 % and 34.0 % higher, respectively, than those in the paclitaxel group. In the cisplatin-induced neurotoxicity model, SOD activity and GSH content exceeded the corresponding values in the cisplatin group by 32.2 % and 46.4 %, respectively.

3. Therapeutic administration of vortioxetine, initiated on day 3 of cytostatic exposure, was likewise associated with changes in the investigated parameters toward the corresponding control values. On day 28, SOD activity and GSH content were 13.3 % and 23.3 % higher, respectively, than those in the paclitaxel group and 20.1 % and 30.5 % higher, respectively, than those in the cisplatin group.

4. The greatest differences between the vortioxetine-treated groups and the corresponding cytostatic-treated groups were observed during the period of maximal redox disturbances. The prophylactic regimen showed a trend toward more favorable values of the investigated parameters than the therapeutic regimen; however, this trend was not supported by statistically significant evidence of superiority.

References

1. Abdel-Wahab WM, Moussa FI. Neuroprotective effect of N-acetylcysteine against cisplatin-induced toxicity in rat brain by modulation of oxidative stress and inflammation. *Drug Des Devel Ther*. 2019;13:1155–1162. doi:10.2147/DDDT.S191240.
2. Akyuz Cim EF, Suleyman Z, Suleyman H, Yazici GN, Coban TA. Effect of sertraline and vortioxetine on stress-induced brain injury in rats: biochemical and histopathological evaluations. *Clin Neuropharmacol*. 2024;47(6):213–217. doi:10.1097/WNF.0000000000000615.
3. Bae EH, Greenwald MK, Schwartz AG. Chemotherapy-induced peripheral neuropathy: mechanisms and therapeutic avenues. *Neurotherapeutics*. 2021;18(4):2384–2396. doi:10.1007/s13311-021-01142-2.
4. dos Santos NAG, dos Santos JM, dos Santos AC. The role of oxidative stress and antioxidant therapy in cisplatin neurotoxicity: preclinical evidence in the last decade. *Arch Toxicol*. 2026;100(6):2285–2305. doi:10.1007/s00204-026-04398-9.
5. Duggett NA, Griffiths LA, McKenna OE, de Santis V, Yongsanguanchai N, Mokori EB, et al. Oxidative stress in the development, maintenance and resolution of paclitaxel-induced painful neuropathy. *Neuroscience*. 2016;333:13–26. doi:10.1016/j.neuroscience.2016.06.050.
6. Kulynych HB, Herashchenko SB, Ostrovskiy MM, Markiv IM, Pertsovych VM, Diachuk OI, et al. Influence of vortioxetine and pioglitazone on neurophysiological manifestations in a rat model of chemotherapy-induced peripheral neuropathy. *World of Medicine and Biology*. 2025;21(93):177–181. doi:10.26724/2079-8334-2025-3-93-177-181.
7. Mattar M, Umutohi F, Hassan MA, Wamburu MW, Turner R, Patton JS, et al. Chemotherapy-induced peripheral neuropathy: a recent update on pathophysiology and treatment. *Life (Basel)*. 2024;14(8):991. doi:10.3390/life14080991.
8. Mert H, Kerem Ö, Mis L, Yıldırım S, Mert N. Effects of protocatechuic acid against cisplatin-induced neurotoxicity in rat brains: an experimental study. *Int J Neurosci*. 2024;134(7):725–734. doi:10.1080/00207454.2022.2147430.
9. Polomano RC, Mannes AJ, Clark US, Bennett GJ. A painful peripheral neuropathy in the rat produced by the chemotherapeutic drug paclitaxel. *Pain*. 2001;94(3):293–304. doi:10.1016/S0304-3959(01)00363-3.
10. Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. *FASEB J*. 2008;22(3):659–661. doi:10.1096/fj.07-9574LSF.
11. Sałat K. Chemotherapy-induced peripheral neuropathy: part 1-current state of knowledge and perspectives for pharmacotherapy. *Pharmacol Rep*. 2020;72(3):486–507. doi:10.1007/s43440-020-00109-y.
12. Samur DN, Akçay G, Yıldırım S, Özkan A, Çeker T, Derin N, et al. Vortioxetine ameliorates motor and cognitive impairments in the rotenone-induced Parkinson's disease via targeting TLR-2 mediated neuroinflammation. *Neuropharmacology*. 2022;208:108977. doi:10.1016/j.neuropharm.2022.108977.
13. Staff NP, Fehrenbacher JC, Caillaud M, Damaj MI, Segal RA, Rieger S. Pathogenesis of paclitaxel-induced peripheral neuropathy: a current review of in vitro and in vivo findings using rodent and human model systems. *Exp Neurol*. 2020;324:113121. doi:10.1016/j.expneurol.2019.113121.
14. Vindya NS, Mohamad A, Razdan R. Allantoin attenuates deficits of behavioural and motor nerve conduction in an animal model of cisplatin-induced neurotoxicity in rats. *Animal Model Exp Med*. 2019;2(2):114–120. doi:10.1002/ame2.12070.
15. Wellenberg A, Brinkmann V, Bornhorst J, Ventura N, Honnen S, Fritz G. Cisplatin-induced neurotoxicity involves the disruption of serotonergic neurotransmission. *Pharmacol Res*. 2021;174:105921. doi:10.1016/j.phrs.2021.105921.

Conflict of interest. The authors have no conflicts of interest to declare.

ORCID: Kulynych H.B. <https://orcid.org/0000-0002-0233-2282>, Ersteniuk H.M. <https://orcid.org/0000-0002-5291-5347>, Herashchenko S.B. <https://orcid.org/0000-0003-0958-4885>, Klishch I.P. <https://orcid.org/0000-0001-6616-1980>, Oliynyk R.P. <https://orcid.org/0000-0002-7586-6664>, Merena S.R. <https://orcid.org/0009-0003-6928-7265>.

Article received: 23.07.2025