Therapeutic Agents for Oxaliplatin-Induced Peripheral Neuropathy; Experimental and Clinical Evidence

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Abstract: Oxaliplatin is an essential drug in the chemotherapy of colorectal, gastric, and pancreatic cancers, but it frequently causes peripheral neuropathy as a dose-limiting factor. So far, animal models of oxaliplatin-induced peripheral neuropathy have been established. The mechanisms of development of neuropathy induced by oxaliplatin have been elucidated, and many drugs and agents have been proven to have neuroprotective effects in basic studies. In addition, some of these drugs have been validated in clinical studies for their inhibitory effects on neuropathy. In this review, we summarize the basic and clinical evidence for the therapeutic effects of oxaliplatin. In basic research, there are many reports of neuropathy inhibitors that target oxidative stress, inflammatory response, sodium channel, transient receptor potential (TRP) channel, glutamate nervous system, and monoamine nervous system. Alternatively, very few drugs have clearly demonstrated the efficacy for oxaliplatin-induced peripheral neuropathy in clinical trials. It is important to activate translational research in order to translate basic research into clinical research.

Keywords: oxaliplatin; peripheral neuropathy; preclinical data; clinical evidence; adverse effects

1. Introduction

Oxaliplatin is a platinum-based chemotherapeutic agent that is widely used as a standard treatment for colorectal, gastric, and pancreatic cancers, usually combined with other therapeutic agents such as fluorouracil, irinotecan, capecitabine, or tegafur, gimeracil and oteracil, however it often causes severe peripheral neuropathy. Within a few hours to a few days after oxaliplatin administration, acute neuropathy, such as cold sensory disturbance in the limbs and perioral region, appears. In most cases, cold-related acute neuropathy is transient and reversible [1,2]. In addition, sensory deficits as chronic neuropathy, a dose-limiting factor, occur after repeated oxaliplatin administration [2,3]. These neuropathies remain a significant clinical problem with oxaliplatin chemotherapy because they can affect quality of life and lead to drug reductions or discontinuation. Previous reports have suggested that voltage-gated ion channels and transient receptor potential channels are involved in oxaliplatin-induced acute neuropathy [4–6]. Chronic neuropathy is thought to be caused by morphological changes in neurons, such as axonal degeneration and damage to neuronal cell bodies [7–9]. However, no drugs have been recommended to prevent chemotherapy-induced peripheral neuropathy [10]. Since around 2000, animal models of chemotherapy-induced peripheral neuropathy, including oxaliplatin-induced...
neuropathy, have been established and reported [11–13]. In this study, we reviewed the preclinical and clinical evidence for oxaliplatin-induced peripheral neuropathy.

2. Therapeutic Agents in Preclinical Evidence

All articles found in PubMed with the search term “oxaliplatin neuropathy or oxaliplatin neurotoxicity” were surveyed. The last search date was 1 August 2020. Reports that did not include information on therapeutic agents for oxaliplatin-induced peripheral neuropathy and clinical studies were excluded from the analysis. From the surveyed papers, we extracted information on the name and dosage of the drugs that showed statistically significant improvement, their mechanism of action, and the animal species in which they were used.

There were 1657 articles in PubMed for the search term “oxaliplatin neuropathy or oxaliplatin neurotoxicity”. Of these, 127 articles reported on drugs that inhibit oxaliplatin-induced peripheral neuropathy in animal studies. The following is a summary of the drugs that had therapeutic effects on oxaliplatin-induced peripheral neuropathy in these basic studies (Table 1).
Table 1. The therapeutic agents for oxaliplatin-induced peripheral neuropathy in preclinical experiments.

| Therapeutic Targets | Therapeutic Agents | Dose     | Animals | Symptoms that Showed Improvement                                                                 | Mechanisms                                                                 | References |
|---------------------|--------------------|----------|---------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|------------|
| Oxidative stress    | Acetyl L-carnitine | 60–150 mg/kg | Rats    | Mechanical, thermal and cold allodynia                                                             | Antioxidant effect                                                       | [14]       |
|                     | Acetyl L-carnitine | 50–100 mg/kg | Rats    | Mechanical, thermal and cold allodynia                                                             | Antioxidant effect                                                       | [15]       |
|                     | Acetyl L-carnitine | 100 mg/kg  | Rats    | Mechanical allodynia                                                                                | Prevention of deficits in mitochondrial function                          | [16]       |
|                     | Alpha-lipoic acid  | 50–100 mg/kg | Rats    | Mechanical, thermal and cold allodynia                                                             | Antioxidant effect                                                       | [15]       |
|                     | Calmangafodipir (PledOx®) | 2.5–10 mg/kg | Mice    | Mechanical allodynia and decrease in IENF density                                                  | Antioxidant effect                                                       | [17]       |
|                     | Carvedilol         | 10 mg/kg   | Rats    | Mechanical and cold allodycia                                                                      | Antioxidant and mitoprotective effects                                   | [18]       |
|                     | Cerium oxide nanoparticles | 60 mg/kg | Rats    | Decrease in MBP of sciatic nerve and increase in GFAP of spinal cord                               | Antioxidant effect                                                       | [19]       |
|                     | Cystine and Theanine | 280 mg/kg | Rats    | Mechanical allodynia and sciatic nervedenervations                                                  | Antioxidant effect (upregulation of glutathione)                         | [20]       |
|                     | Dimethyl fumarate  | 200 mg/kg | Rats    | Mechanical allodynia and sciatic nervedenervations                                                  | Antioxidant effect                                                       | [21]       |
|                     | Donepezil          | 1 mg/kg    | Rats    | Mechanical allodynia                                                                                | Recovery of reduction in SOD activity                                   | [22]       |
|                     | Glutathione        | 33 mg/kg   | Mice    | Cold allodynia                                                                                     | Aluminum chelation and antioxidative effect                               | [23]       |
|                     | Lycopene           | 2–4 mg/kg  | Rats    | Neurodegenerative changes (increases in NCAM and BDNs), and decreases in GFAP and caspase-3 in brain and sciatic nerve | Antioxidative effects (downregulation of SOD, CAT, and GP’s), and antiinflammatory effects (downregulation of MAPK14, NF-κB and TNF-α) | [24]       |
|                     | Melatonin          | 10 mg/kg   | Rats    | Locomotor activity, muscular strength, thermal, and mechanical allodynia                            | Antioxidative effects and inactivations of Bcl-2, caspase 3 apoptotic protein and alterations Cytochrome c release Inhibition of nitration and activation of superoxide dismutase in mitochondria, and increase in ATP production in primary nerve sensory axons | [25]       |
|                     | Mn(III) 5,10,15,20-tetrakis(N-n-hexylpyridinium-2-yl)porphyrin (MnTE-2-PyP(5+)) | 0.3–3 mg/kg | Rats    | Mechanical allodynia                                                                                | Antioxidative effects and inactivations of caspase 3/7 in astrocyte       | [26]       |
|                     | MnL4 (SOD mimetic compound) | 15 mg/kg | Rats    | Motor coordination, mechanical and cold allodynia                                                  | Antioxidative and antiinflammatory effects                                | [27]       |
|                     | Niclosamide        | 10 mg/kg   | Mice    | Tactile hypoesthesia and thermal hyperalgesia, IENF density, and demyelination                      | Antioxidative and antiinflammatory effects                                | [28]       |
| Therapeutic Targets | Therapeutic Agents | Dose       | Animals | Symptoms that Showed Improvement | Mechanisms                                                                 | References |
|---------------------|--------------------|------------|---------|----------------------------------|-----------------------------------------------------------------------------|------------|
| Oxidative stress    | Phosphatidylcholine| 300 mg/kg  | Rats    | Mechanical and thermal alldynia   | Antioxidative effects (downregulation of malondialdehyde, glutathione, GPx, and SOD in sciatic nerve) and modulation of microglial activities | [29]       |
|                     | Quercetin          | 20 mg/kg   | Mice    | Mechanical alldynia              | Antioxidant effect                                                          | [30]       |
|                     | Quercetin          | 25–100 mg/kg | Mice  | Mechanical and cold alldynia     | Downregulation of nitric oxide and peroxynitrite                            | [31]       |
|                     | Resveratrol        | 100 mg/kg  | Mice    | Mechanical alldynia              | Antioxidant effect                                                          | [30]       |
|                     | Rosiglitazone      | 3–10 mg/kg | Rats    | Mechanical, cold alldynia and motor coordination | Prevention of catalase impairment                                            | [32]       |
|                     | Rutin              | 20 mg/kg   | Mice    | Mechanical alldynia              | Antioxidant effect                                                          | [30]       |
|                     | Rutin              | 25–100 mg/kg | Mice | Mechanical and cold alldynia     | Downregulation of nitric oxide and peroxynitrite                            | [31]       |
|                     | Silibinin          | 100 mg/kg  | Rats    | Mechanical and cold alldynia     | Improvement of oxidative alterations                                        | [34]       |
|                     | SS-20 (mitochondria-targeted peptide) | 5–10 mg/kg | Mice | Mechanical alldynia and IENF density | Mitochondrial protection                                                    | [35]       |
|                     | SS-31              | 5 mg/kg    | Mice    | Mechanical and cold alldynia     | Mitochondria-targeted antioxidant                                            | [36]       |
|                     | Sulforaphane       | 5 mg/kg    | Mice    | Mechanical alldynia and morphological alterations, mitochondrial dysfunction in DRG | Activation of the Nrf2 signaling pathway                                    | [37]       |
|                     | Vitamin C          | 50–100 mg/kg | Rats | Mechanical and cold alldynia     | Antioxidant effect                                                          | [15]       |
|                     | Vitis vinifera extract | 300 mg/kg | Rats    | Mechanical and cold alldynia     | Antioxidant effect                                                          | [38]       |
|                     | α-tocopherol       | 100 mg/kg  | Rats    | Mechanical and cold alldynia     | Improvement of oxidative alterations                                        | [34]       |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|--------------------|------|---------|----------------------------------|------------|-------------|
| Inflammatory        | Bee Venom derived phospholipase A<sub>2</sub> | 0.2 mg/kg | Mice | Mechanical and cold allodynia | Suppression of infiltration of macrophages and the increase in IL-1β level in the DRG | [39] |
|                     | Fluorocitrate      | 1 nmol/h (i.t.) | Rats | Mechanical allodynia | Inactivation of microglia | [40] |
|                     | Herbal Medicine AC591 | 10,000–20,000 mg/kg | Rats | Mechanical, cold allodynia, and histological changes in sciatic nerve and DRG | Downregulation of inflammation and immune response | [41] |
|                     | Houttuynia cordata Thunb | 1000 mg/kg | Rats | Mechanical allodynia | Modulation of Th17/Treg balance by regulating PI3K/Akt/mTOR signaling pathway | [42] |
|                     | Minocycline        | 12.5 nmol/h (i.t.) | Rats | Mechanical allodynia | Inactivation of astrocyte | [40] |
|                     | Minocycline        | 25 mg/kg | Rats | Mechanical allodynia | Inactivation of astrocyte | [43] |
|                     | Rapamycin          | 5 mg/kg | Rats | Mechanical and cold allodynia | Blocking mTOR and decreases in IL-1β, IL-6, and TNF-α | [44] |
| Na channel          | Lidocaine          | 30 mg/kg | Rats | Cold allodynia | N/A | [45] |
|                     | Lidocaine          | 3–10 mg/kg | Rats | Cold allodynia | N/A | [11] |
|                     | Mexiletine         | 100 mg/kg | Rats | Cold allodynia | N/A | [45] |
|                     | Mexiletine         | 30 mg/kg | Mice | Cold allodynia | N/A | [46] |
|                     | Lacosamide         | 10–30 mg/kg | Mice | Mechanical allodynia | N/A | [47] |
|                     | Lamotrigine        | 5–10 mg/kg | Mice | Cold allodynia | N/A | [48] |
|                     | Bromhexine         | 150 mg/kg | Mice | Tactile, cold allodynia | Inhibition of Nav1.6, Nav1.7, and Nav1.9 | [49] |
| Glucosinolate glucoraphanin | 4.43–119.79 µmol/kg | Mice | Mechanical allodynia | Releasing H<sub>2</sub>S and modulating Kv<sub>7</sub> channels | [50] |
| K channel           | Isothiocyanate sulforaphane | 1.33–13.31 µmol/kg | Mice | Mechanical allodynia | Releasing H<sub>2</sub>S and modulating Kv<sub>7</sub> channels | [50] |
|                     | Allyl-isothiocyanate | 1.33–13.31 µmol/kg | Mice | Cold allodynia | Releasing H<sub>2</sub>S and modulating Kv<sub>7</sub> channels | [51] |
|                     | Phenyl- and carboxyphenyl-isothiocyanate | 1.33–13.31 µmol/kg | Mice | Cold allodynia | Releasing H<sub>2</sub>S and modulating Kv<sub>7</sub> channels | [51] |
|                     | Riluzole           | 7.5 mg/kg | Mice | Mechanical and cold allodynia | Releasing H<sub>2</sub>S and modulating Kv<sub>7</sub> channels | [51] |
|                     | Gabapentin         | 10–100 mg/kg | Mice | Mechanical alldodynia | Involvement of TREK-1 potassium channel | [52] |
| Ca channel          | Gabapentin         | 100 mg/kg | Mice | Cold allodynia | N/A | [48] |
|                     | Gabapentin         | 30 mg/kg | Mice | Cold allodynia | N/A | [46] |
|                     | Gabapentin         | 300 mg/kg | Rats | Cold allodynia | N/A | [11] |
|                     | Pregabalin         | 30 mg/kg | Rats | Mechanical and cold allodynia | Attenuation of cofilin phosphorylation in spinal cord | [53] |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|--------------------|------|---------|---------------------------------|------------|------------|
| TRP channel         | Topiramate         | 50 mg/kg | Mice | Cold allodynia | Prevention of cytosolic acidification and TRPA1 and TRPV1 modulation in DRG neurons | [55] |
|                     | Acetazolamide      | 50 mg/kg | Mice | Cold allodynia | Prevention of cytosolic acidification and TRPA1 and TRPV1 modulation in DRG neurons | [55] |
|                     | Shakuyakukanzoto   | 100–1000 mg/kg | Mice | Cold allodynia | Inhibition of TRPM8 expression in DRG | [56] |
|                     | Goshajinkigan      | 300–1000 mg/kg | Rats | Cold allodynia | Suppressions of increases in TRPA1 and TRPM8 in DRG | [57] |
|                     | Goshajinkigan      | 1000 mg/kg | Rats | Cold allodynia | Suppressions of increases in TRPA1 and TRPM8 in DRG | [58] |
|                     | Eel calcitonin     | 20 U/kg | Rats | Cold allodynia | Inhibition cellular signaling related to TRPA1 and TRPM8 | [59] |
| HCN1/HCN2           | Nifedipine         | 10–30 mg/kg | Rats | Cold allodynia | Downregulation of TRPM8 | [60] |
|                     | Diltiazem          | 10–30 mg/kg | Rats | Cold allodynia | Downregulation of TRPM8 | [60] |
|                     | Mexiletine         | 10–30 mg/kg | Rats | Cold allodynia | Downregulation of TRPM8 | [60] |
|                     | MEL57A             | 1–10 mg/kg | Rats | Mechanical allodynia | Blockade of HCN1/HCN2 Channels | [62] |
|                     | MEL55A             | 30 mg/kg | Rats | Cold allodynia | Blockade of HCN1/HCN2 Channels | [62] |
| Imidazoline receptor| 2-(1-([1,1’-biphenyl]-2-yl)propan-2-yl)-4,5-dihydro-1H-imidazole (carbophenyline) | 0.1–10 mg/kg | Mice | Mechanical, cold allodynia, and increase in GFAP of spinal cord | I1-imidazoline receptor agonist | [63] |
|                     | Riluzole           | 12 mg/kg | Rats | Mechanical allodynia | Suppression of increase in glutamate concentration and decrease in GLT-1 in spinal cord | [64] |
|                     | Dimiracetam        | 100–300 mg/kg | Rats | Mechanical allodynia | Counteraction of NMDA-induced release of glutamate with highest potency in the spinal cord | [65] |
|                     | E2072              | 0.1–1 mg/kg | Mice | Mechanical allodynia | Glutamate carboxypeptidase II inhibitor | [66] |
| Glutamate           | Tat-HA-NR2B9c      | 50–100 ng (i.t.) | Mice and rats | Mechanical and cold allodynia | NMDA receptor antagonist | [67] |
|                     | Mirtazapine        | 20–30 mg/kg | Rats | Mechanical allodynia | Downregulation of NMDA receptor NR2B subunit | [68] |
|                     | Ifenprodil         | 50 mg/kg | Rats | Mechanical allodynia | NMDA receptor antagonist | [69] |
|                     | Amitriptyline      | 5–10 mg/kg | Rats | Mechanical allodynia | Downregulation of NMDA receptor NR2B subunit | [70] |
|                     | Trifluoperazine    | 0.3 mg/kg | Rats | Mechanical allodynia | Inhibition of CaMKII | [71] |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|--------------------|--------------------|------|---------|----------------------------------|------------|------------|
| PDE                | Tadalafil          | 10 mg/kg | Mice    | Cold, mechanical, and electrical current hypersensitivities, and thermal hypoesthesia. | Increases in blood flow and skin temperature | [72]       |
|                    | Ibudilast          | 7.5 mg/kg | Rats    | Mechanical allodynia             | N/A        | [73]       |
|                    | Bosentan           | 100 mg/kg | Mice    | Mechanical and thermal hypersensitivity | Antagonism of endothelin ETA and ETB receptors | [74]       |
| Endothelin receptor |                    |        |         |                                  |            |            |
| Cannabinoid receptor | Cannabidiol      | 1.25–10 mg/kg | Mice    | Mechanical allodynia             | N/A        | [75]       |
|                    | E-52862            | 20–80 mg/kg | Rats    | Cold allodynia                   | Sigma-1 receptor antagonist | [76]       |
|                    | SA4503             | 3 mg/kg | Rats    | Mechanical allodynia             | Sigma-1 receptor agonist | [77]       |
|                    | Fentanyl           | 0.017–0.03 mg/kg | Rats    | Mechanical and cold allodynia    | N/A        | [78]       |
|                    | LOR17 (κ-opioid receptor agonist) | 1–20 mg/kg | Rats    | Cold allodynia                   | κ-opioid receptor agonist | [79]       |
|                    | Morphine           | 1–3 mg/kg | Rats    | Mechanical and cold allodynia    | N/A        | [78]       |
|                    | Oxycodone          | 0.3–0.56 mg/kg | Rats    | Mechanical and cold allodynia    | N/A        | [78]       |
|                    | Tramadol           | 20 mg/kg | Mice    | Cold allodynia                   | N/A        | [46]       |
|                    | Tramadol           | 30 mg/kg | Rats    | Cold allodynia                   | N/A        | [80]       |
|                    | Amitriptyline      | 2.5–10 mg/kg | Mice    | Cold allodynia                   | N/A        | [81]       |
|                    | Bee venom          | 0.1 mg/kg | Mice    | Mechanical allodynia and IENF density | Activation of the noradrenergic system, via α2-adrenergic receptors | [82]       |
|                    | Bee venom acupuncture | 0.25–2.5 mg/kg | Mice    | Mechanical and cold allodynia    | Activations of spinal opioidergic and 5-HT3 receptors | [83]       |
|                    | Bee venom acupuncture | 0.25–1 mg/kg | Rats    | Cold allodynia                   | Activation of the noradrenergic system | [84]       |
|                    | Bee Venom derived phospholipase A₂ | 0.2 mg/kg | Mice    | Mechanical and cold allodynia    | Activation of the noradrenergic system, via α2-adrenergic receptors | [85]       |
|                    | Clonipramine       | 2.5 mg/kg | Rats    | Cold allodynia                   | N/A        | [86]       |
|                    | Clonidine          | 0.1 mg/kg | Mice    | Mechanical allodynia and spinal p-p38 MAPK expression | α2 adrenoceptor agonist | [86]       |
| Monoamines         | Duloxetine         | 30–60 mg/kg | Mice    | Mechanical and cold allodynia    | Activating spinal α1-adrenergic receptor | [87]       |
|                    | Duloxetine         | 30 mg/kg | Rats    | Cold allodynia                   | N/A        | [80]       |
|                    | Duloxetine         | 2.5 mg/kg | Mice    | Cold allodynia                   | N/A        | [88]       |
|                    | Fluoxetine         | 20 mg/kg | Rats    | Mechanical and cold allodynia    | Blockade serotonergic 5-HT2C receptor | [89]       |
|                    | Melittin (major content of bee venom) | 0.5 mg/kg | Mice    | Mechanical and cold allodynia    | Activating the spinal α₁- and α₂-adrenergic receptors. | [90]       |
|                    | Morphine           | 2–5 mg/kg | Mice    | Mechanical and cold allodynia    | Activations of spinal opioidergic and 5-HT4 receptors | [83]       |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|--------------------|------|---------|-----------------------------------|------------|------------|
| **Monoamines**      | NLX-112            | 0.1–5 mg/kg | Mice | Mechanical allodynia             | 5-HT<sub>1A</sub> receptor agonist | [91]       |
|                     | pregabalin         | 30 mg/kg   | Rats  | Cold allodynia                    | N/A        | [80]       |
|                     | scolopendra subspinipes | 0.5%/20 µL (acupoint treatment) | Mice | Mechanical allodynia              | Activation of spinal α<sub>2</sub>-adrenoceptor | [92]       |
|                     | tandospirone       | 1–3 mg/kg  | Mice  | Mechanical allodynia and mast cell migration | 5-HT<sub>1A</sub> receptor agonist | [93]       |
|                     | venlafaxine        | 7.5 mg/kg  | Rats  | Cold allodynia                    | N/A        | [11]       |
|                     | vortioxetine       | 1–10 mg/kg | Mice  | Mechanical and cold allodynia     | Increases in NA and 5HT in brain | [94]       |
|                     | xaliproden         | 0.3–3 mg/kg | Mice | Mechanical allodynia and mast cell migration | 5-HT<sub>1A</sub> receptor agonist | [93]       |
| **Acetylcholine receptor** | citicoline        | 1–2 µmol (i.c.v.) | Rats | Mechanical allodynia              | Involvement of α7 nAChRs, and interaction between GABAergic and cholinergic system | [95]       |
|                     | (R)-ICH3           | 30 mg/kg   | Rats  | Mechanical and cold allodynia     | α7 nAChR agonist | [96]       |
|                     | PNU-282987         | 30 mg/kg   | Rats  | Mechanical and cold allodynia     | α7 nAChR agonist | [96]       |
|                     | αα-Conotoxin GeXIVA 1,2 | 32–128 mg/kg | Rats | Mechanical and cold allodynia     | Antagonism of the α9α10 nAChR | [97]       |
|                     | αα-conotoxin RgIA  | 2–10 nmol (i.m.) | Rats | Mechanical, cold allodynia, and morphological changes of DRG | α9α10 nAChR agonist | [98]       |
| **OCT2**            | dasatinib          | 15 mg/kg   | Mice  | Mechanical allodynia              | Inhibition of platinum accumulation via OCT2 | [99]       |
| **OCTN1**           | ergothioneine      | 15 mg/kg   | Rats  | Mechanical allodynia              | Inhibition of OCTN1 and decrease in platinum accumulation in DRG neurons. | [100]      |
| **Histamine receptor** | orexin-A           | 0.1–1 nmol (i.c.v.) | Mice | Mechanical allodynia              | Orexin type-1 receptor agonist | [101]      |
|                     | S 38093            | 0.3–3 mg/kg | Rats | Cold allodynia                    | Histamine H3 receptor agonist | [102]      |
| **PKC/MEK/ERK**     | trametinib         | 0.5 mg/kg  | Mice  | Mechanical and cold allodynia     | Inhibition of the MEK/ERK pathway | [103]      |
|                     | tamoxifen          | 10–30 mg/kg | Mice | Mechanical and cold allodynia     | Inhibition of PKC/ERK/c-Fos pathway in spinal cord | [104]      |
|                     | PD0325901          | 10–30 mg/kg | Mice | Mechanical and cold allodynia     | Inhibition of MEK1/2 | [104]      |
| **Ceramide-sphingosine 1-phosphate** | FTY720            | 0.01 mg/kg | Rats | Mechanical allodynia              | Modulation of ceramide-S1P R1 | [105]      |
| Therapeutic Targets | Therapeutic Agents | Dose          | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|-------------------|--------------|---------|----------------------------------|------------|------------|
| **Oxalate**         | Calcium gluconate | 0.5 mmol/kg  | Mice    | Cold allodynia                   | N/A        | [46]       |
|                     | Calcium           | 0.5 mmol/kg  | Rats    | Cold allodynia                   | N/A        | [13]       |
|                     | Magnesium         | 90 mg/kg     | Rats    | Cold allodynia                   | N/A        | [11]       |
|                     | Magnesium         | 0.5 mmol/kg  | Rats    | Cold allodynia                   | N/A        | [13]       |
| **Thrombin activity**| Thrombomodulin alfa | 0.1–1 mg/kg  | Rats    | Mechanical allodynia             | Activation of TAFI and protein C by modulating thrombin activity | [106]     |
|                     | Warfarin          | 1 mg/kg      | Mice and rats | Mechanical allodynia             | Upregulation of HMGB1 | [107]     |
|                     | Dabigatran        | 75 mg/kg     | Mice and rats | Mechanical allodynia             | Upregulation of HMGB1 | [107]     |
|                     | Rivaroxaban       | 10 mg/kg     | Mice and rats | Mechanical allodynia             | Upregulation of HMGB1 | [107]     |
| **VEGF**            | Bevacizumab       | 1–15 mg/kg   | Rats    | Mechanical and cold allodynia    | Anti VEGF-A effect | [108]     |
|                     | 17α-hydroxyprogesterone caproate | 10 mg/kg  | Rats    | Mechanical and cold allodynia    | Reduction of ATF-3, c-Fos, GFAP, Iba-1, IL-1β and TNFα in DRG and spinal cord | [109]     |
|                     | Allopregnanolone  | 4 mg/kg      | Rats    | Mechanical and cold allodynia    | Motor dysfunction and electrophysiological assessment of motor nerves | N/A       | [110]     |
|                     | Alogliptin        | 10 mg/kg     | Rats    | Mechanical alldodynia and sciatic nerve degeneration | Neuroprotective effects | [111]     |
|                     | Aqueous extract of Forsythia viridissima | 100 mg/kg | Mice    | Mechanical allodynia and decrease in IENF density | N/A        | [112]     |
|                     | Aqueous extract of Forsythiae suspensa fruits | 50–100 mg/kg | Mice    | Mechanical allodynia and decrease in IENF density | N/A        | [113]     |
| **Others**          | Aqueous extract of Lithospermi Radix | 250 mg/kg   | Mice    | Mechanical allodynia             | N/A        | [114]     |
|                     | Aripiprazole      | 10 mg/kg     | Mice    | Mechanical allodynia             | N/A        | [115]     |
|                     | Astragali radix   | 100–300 mg/kg| Rats    | Mechanical and thermal allodynia | N/A        | [116]     |
|                     | Benztropine       | 10 mg/kg     | Mice    | Mecahnical, cold alldodynia, and demyelination in sciatic nerve | N/A        | [117]     |
|                     | Ceftriaxone       | 200 mg/kg    | Mice    | Mechanical allodynia             | N/A        | [115]     |
| Therapeutic Targets | Therapeutic Agents | Dose | Animals | Symptoms that Showed Improvement | Mechanisms | References |
|---------------------|--------------------|------|---------|---------------------------------|------------|------------|
|                     | Cinnamomi Cortex   | 100–400 mg/kg | Rats    | Cold allodynia                  | Attenuation of spinal microglia and astrocyte, and downregulation of IL-1β and TNF-α | [118]       |
|                     | Cryptotanshinone   | 10–30 mg/kg  | Mice    | Cold allodynia                  | N/A        | [119]       |
|                     | Curcumin           | 10 mg/kg     | Rats    | Neurodegeneration in sciatic nerve | Downregulation of neurotensin and platinum concentrations in sciatic nerve | [120]       |
|                     | Elcatonin          | 20 U/kg      | Rats    | Mechanical and cold allodynia   | N/A        | [54]        |
|                     | Exenatide          | 0.1 mg/kg    | Rats    | Mechanical and cold alldodynia  | Neuroprotective effects | [121]       |
|                     | Fulvestrant        | 5–10 mg/kg   | Rats    | Mechanical alldodynia and sciatic nervenedenegerations | Neuroprotective effects | [122]       |
|                     | Goshajinkigan      | 300–1000 mg/kg | Mice  | Mechanical and cold alldodynia  | N/A        | [123]       |
|                     | Goshajinkigan      | 300–1000 mg/kg | Rats  | Mechanical and cold alldodynia  | N/A        | [124]       |
| Others              | Hirudin            | 10 mg/kg     | Mice    | Mechanical alldodynia           | Downregulation of p38, HIF-1α and MMP-9/2 | [125]       |
|                     | HM01               | 10–30 mg/kg  | Rats    | Nerveconduction velocity of digital nerve, caudal nerve and IENF density | Ghrelin agonist | [126]       |
|                     | Melatonin          | 3–10 mg/kg   | Mice    | Mechanical and cold alldodynia  | Antioxidant effect, improvement of mitochondrial function, activation of autophagy pathway, and anti-apoptotic effect | [127]       |
|                     | Metformin          | 250 mg/kg    | Rats    | Mechanical, cold alldodynia     | N/A        | [128]       |
|                     | Metformin          | 250 mg/kg    | Mice    | Mechanical alldodynia           | Decreases in ATF-3 and c-Fos expressions in spinal cord and DRG | [129]       |
|                     | Neurotropin (a non-protein extract derived from the inflamed skin of rabbits inoculated with vaccinia virus) | 100–200 U/kg | Rats    | Mechanical and cold alldodynia  | Monoaminergic descending pain inhibitory system via Gi protein-coupled receptors | [130]       |
|                     | Neurotropin (a non-protein extract derived from the inflamed skin of rabbits inoculated with vaccinia virus) | 200 U/kg    | Rats    | Mechanical alldodynia           | Neuroprotective effects | [131]       |
Table 1. Cont.

| Therapeutic Targets | Therapeutic Agents                        | Dose         | Animals | Symptoms that Showed Improvement | Mechanisms                                                                 | References |
|---------------------|-------------------------------------------|--------------|---------|----------------------------------|---------------------------------------------------------------------------|------------|
| Ninjin’yoeito       | 1000 mg/kg                                 | Mice         | Mechanical and cold allodynia    | N/A                                                                        | [132]      |
| Palmitoylethanolamine| 30 mg/kg                                   | Rats         | Mechanical and cold allodynia    | Neuroprotective effects and glia-activation prevention                     | [133]      |
| Phenytoin           | 5–10 mg/kg                                 | Mice         | Cold allodynia                   | N/A                                                                        | [48]       |
| Processed aconite root| 1000 mg/kg                                 | Mice         | Mechanical and cold allodynia    | N/A                                                                        | [134]      |
| Retigabine          | 5–10 mg/kg                                 | Mice         | Cold allodynia                   | N/A                                                                        | [48]       |
| Salmon calcitonin   | 20 U/kg                                    | Rats         | Mechanical and cold allodynia    | N/A                                                                        | [135]      |
| Salvia miltiorrhiza | 300–600 mg/kg                              | Mice         | Cold allodynia                   | N/A                                                                        | [119]      |
| Tanshinone IIA      | 25 mg/kg                                   | Rats         | Mechanical, cold allodynia, and demyelination in sciatic nerve | Mitochondrial protection and autophagy promotion | [136]      |
| Tanshinone IIA      | 10 mg/kg                                   | Mice         | Cold allodynia                   | N/A                                                                        | [119]      |
| Topiramate          | 100 mg/kg                                  | Rats         | Mechanical allodynia             | N/A                                                                        | [137]      |
| Water extract of Lepidium meynii root| 10,000 mg/kg | Rats         | Mechanical allodynia             | N/A                                                                        | [138]      |
| Wen-luo-tong        | Paws and tails were soaked in 0.6 g/mL solution for 20 min | Rats         | Mechanical allodynia             | Reductions of histological dischange in DRG and glial activation in the spinal dorsal horn | [139]      |

Abbreviations: 5-HT, serotonin; Akt, protein kinase B; ATF-3, activating transcription factor 3; ATP, adenosine triphosphate; CAT, catalase; CaMKII, calmodulin-dependent protein kinase II; DRG, dorsal root ganglia; ERK, extracellular signal-regulated kinase; ETA, endothelin A; ETB, endothelin B; GFAP, glial fibrillary acidic protein; GLT-1, glutamate transporter 1; GPx, glutathione peroxidase; IHC1, hyperpolarization-activated, cyclic nucleotide-gated cation channel 1; IHC1, hyperpolarization-activated, cyclic nucleotide-gated cation channel 2; HEF-1, hypoxia inducible factor 1; HMGB1, high mobility group box 1; Iba-1, ionized calcium binding adaptor protein 1; i.c.v., intracerebroventricular; IENF, intra-epidermal nerve fibers; IL-1β, interleukin-1 beta; IL-6, interleukin-6; i.m., intramuscular; i.t., intrathecal; MAPK14, mitogen-activated protein kinase-14; MBF, myelin basic protein; MEK1/2, mitogen-activated protein kinase kinases 1 and 2; MMP9/2, matrix metalloproteinase-9 and -2; mTOR, mammalian target of rapamycin; nAChR, nicotinic acetylcholine receptor; NF-κB, nuclear factor kappa-B; NMDA, N-methyl-D-aspartate; OCT2, organic cation transporter 2; OCTN1, organic cation transporter novel type 1; PDE, phosphodiesterase; P38, phosphatidylinositol-3 kinase; PKC, protein kinase C; SOD, superoxide dismutase; S1P, sphingosine-1-phosphate; TAFI, thrombin-activatable fibrinolysis inhibitor; TNF-α, tumor necrosis factor-α; TREK-1, tandem pore domains in weak rectifying K+ channel (TWIK)-related K+ channel 1; TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential melastatin 8; TRPV1, transient receptor potential vanilloid 1; VEGF, vascular endothelial growth factor.
2.1. Antioxidants

Many previous preclinical reports support that oxidative stress plays a role in oxaliplatin-related peripheral neuropathy [27,140,141]. Vitamin C, vitamin E, acetyl L-carnitine, alpha-lipoic acid, and glutathione, which are widely known for their antioxidant effects, have been reported to alleviate the peripheral neuropathy of oxaliplatin in rodents [14–16,23,34]. Among the approved drugs, carvedilol, donepezil, dimethyl fumarate, and rosiglitazone have also been reported to reverse the neurotoxicity of oxaliplatin via their antioxidant effects [18,21,22,32]. Moreover, many agents, which have antioxidant effects, inhibit oxaliplatin-caused peripheral neuropathy in preclinical studies [17,19,20,24–26,28–31,33,35–38].

2.2. Anti-Inflammatory Agents

Inflammatory cytokines such as IL-1β, IL-6, and TNF-α were elevated in the dorsal root ganglion (DRG) and spinal cord of oxaliplatin-treated animals, and some agents reduced the peripheral neuropathy symptoms via their anti-inflammatory effects [39,41,42]. Activations of astrocytes and microglia were also observed in the spinal dorsal horn after oxaliplatin administrations, and minocycline, rapamycin, and fluorocitrate inhibited these spinal changes and prevented neurological damage [40,43,44].

2.3. Sodium Channel Inhibitors

Oxaliplatin-induced acute neuropathy is termed a ‘channelopathy’, as oxaliplatin and oxalate modulated voltage-gated Na⁺ and K⁺ channels in several types of neurons [3,142,143]. For example, oxaliplatin increases the amplitude and duration of compound action potentials interacting with voltage-gated Na⁺ channels in rat sensory neurons [142]. Furthermore, oxaliplatin prolongs the duration of the A-fiber compound action potential related to K⁺ channels [3]. Thus, the effect of oxaliplatin on Na⁺ and K⁺ channels is thought to be involved in acute neuropathy [4]. Many Na⁺ channel inhibitors, such as lidocaine, mexiletine, and lamotrigine have been reported to ameliorate the neuropathic symptoms of oxaliplatin, especially the acute neuropathy [11,45–49].

2.4. Potassium Channel Modulators

Glucosinolate glucoraphanin, isothiocyanate sulforaphane, allyl-isothiocyanate, phenylisothiocyanate and carboxyphenyl-isothiocyanate inhibited oxaliplatin-induced neuropathy by modulating Kv7 channels [50,51]. It has been reported that tandem pore domains in weak rectifying K⁺ channel (TWIK)-related K⁺ channel 1 (TREK-1) channels are partially involved in the inhibitory effect of riluzole on oxaliplatin-induced peripheral neuropathy [52].

2.5. Calcium Channel α2δ Ligands

In animal studies only, gabapentin and pregabalin, which act on α2δ, reduced the symptoms of oxaliplatin neuropathy [11,46,48,53,54].

2.6. Transient Receptor Potential (TRP) Modulators

It has been reported that temperature-sensitive cation channels, such as transient receptor potential ankyrin 1 (TRPA1), transient receptor potential melastatin 8 (TRPM8), and transient receptor potential vanilloid 1 (TRPV1), are involved in oxaliplatin-induced peripheral neuropathy [144–146]. It has also been reported that the amelioration of oxaliplatin neuropathy by topiramate, acetazolamide, shakuyakukanzoto, goshajinkigan, eel calcitonin, nifedipine, diltiazem, and mexiletine, is partly due to the downregulation or modulation of TRP channels [55–56].

2.7. Modulators of Glutamate Nervous System

Some studies indicated that the excessive spinal transmission activities, such as spinal glutamate uptake and spinal N-methyl-D-aspartate receptor subtype NR2B subunit over-expression, are involved in painful neuropathic symptoms related to oxaliplatin [64,69,71]. Riluzole, mirtazapine, ifenprodil, amitriptyline, trifluoperazine, dimiracetam, E2072, and
Tat-HA-NR2B9c targeted these glutamatergic nervous systems and showed that oxaliplatin reduced neurotoxicity [64–71].

2.8. Modulators of Monoamine Nervous System

Monoamines, including noradrenalin and serotonin, play an important role in the descending pain inhibitory system [147]. In also the oxaliplatin peripheral neuropathy animal models, many drugs, such as, duloxetine, fluoxetine, vortioxetine, tandospirone, venlafaxine, xaliproden, clomipramine, and clonidine, also showed analgesic effects by modulating the monoamine nervous system [11,80–94].

2.9. Others

In addition to the above, many other drugs have been identified to reduce oxaliplatin-induced peripheral neuropathy via several therapeutic targets, such as acetylcholine receptors [95–98], thrombin [106,107], protein kinase C/mitogen-activated protein kinase and extracellular signal-regulated kinase signal [103,104], organic cation transporter [99,100], opioid receptors [46,78–80], phosphodiesterase [72,73], hyperpolarization-activated, cyclic nucleotide-gated cation channel [61,62], imidazoline receptors [63], endothelin receptor [74], cannabinoid receptors [75], sigma-1 receptors [76,77], orexin receptors [101], histamine receptors [102], ceramide-sphingosine 1-phosphate [105], chelate of oxalate [11,13], vascular endothelial growth factor [108], and others [48,54,109–139], at the basic research.

3. Therapeutic Agents in Clinical Evidence

We analyzed the articles found in PubMed with the search term “oxaliplatin neuropathy or oxaliplatin neurotoxicity” limited to “clinical trials”. The last search date was 25 June 2020. Reports other than randomized trials and meta-analyses were excluded. Moreover, Information such as the investigational drug and its dosage, chemotherapy received by the patient, study design, number of patients, and results was collected.

There were 533 articles in PubMed for the search term “oxaliplatin neuropathy or oxaliplatin neurotoxicity” limited to “clinical trials”. Of these, 127 articles reported on drugs that inhibit oxaliplatin-induced peripheral neuropathy in animal studies. After excluding reports other than randomized trials and meta-analyses, the authors found 16 reports that they considered to be clinically important. A summarized list of the representative randomized controlled trials and meta-analyses on prophylactic and therapeutic agents for oxaliplatin-induced peripheral neuropathy is shown below in Table 2.
| Investigational Drug | Dose | Chemotherapy | Study Design | Patient Number | Summary | References |
|----------------------|------|--------------|--------------|----------------|---------|------------|
| **Duloxetine**       | 60 mg/day (30 mg/day for the first week) | Taxane or platinum | Randomized, double-blind, placebo-controlled, cross-over | 231 | RRs (95% CI) of experiencing 30% and 50% pain reduction were 1.96 (1.15–3.35) and 2.43 (1.11–5.30), respectively. | [148] |
| Calcium gluconate, 1 g; magnesium sulfate, 1 g (pre- and post-oxaliplatin) | Oxaliplatin | Randomized, double-blind, placebo-controlled | 102 | Significant improvements in incidence of ≥ Grade 2 neuropathy, oxaliplatin-specific scale, and acute muscle spasms | [149] |
| Calcium gluconate, 1 g; magnesium sulfate, 1 g (pre- and post-oxaliplatin) | Oxaliplatin | Randomized, double-blind, placebo-controlled | 139 | No significant differences in time to treatment discontinuation | [150] |
| Calcium gluconate, 1 g; magnesium sulfate, 1 g (pre- and post-oxaliplatin) | Oxaliplatin | Randomized, double-blind, placebo-controlled | 353 | No significant differences compared to placebo group | [151] |
| Calcium gluconate, 1 g; magnesium sulfate, 1 g (pre- and post-oxaliplatin) | Oxaliplatin | Randomized, double-blind, placebo-controlled, cross-over | 19 | No significant differences compared to placebo group | [152] |
| **Calcium and magnesium** | N/A | Oxaliplatin | Meta-analysis | 694 | No significant differences compared to control group RRs (95% CI) of the incidence of ≥ Grade 2 neuropathy and ≥ Grade 1 chronic neuropathy were 0.81 (0.60–1.11) and 0.95 (0.69–1.32), respectively. | [153] |
| **Goshajinkigan**    | 7.5 g/day | Oxaliplatin | Randomized, controlled | 45 | Significant improvement in incidence of ≥ Grade 2 neuropathy compared control group | [154] |
| 7.5 g/day | Oxaliplatin | Randomized, double-blind, placebo-controlled | 93 | No significant differences compared to placebo group | [155] |
| 7.5 g/day | Oxaliplatin | Randomized, double-blind, placebo-controlled | 188 | Significant increase in incidence of ≥ Grade 2 neuropathy compared placebo group | [156] |
| **Alpha–lipoic acid** | 1800 mg/day | Cisplatin or oxaliplatin | Randomized, double-blind, placebo-controlled | 243 | No significant differences compared to placebo group for FACT/GOG-Ntx scores, BPI scores, and patients’ functional outcomes. | [157] |
### Table 2. Cont.

| Investigational Drug | Dose               | Chemotherapy      | Study Design                          | Patient Number | Summary                                                                                     | References |
|-----------------------|--------------------|-------------------|---------------------------------------|----------------|---------------------------------------------------------------------------------------------|------------|
| Vitamin E             | 400 mg/day         | Oxaliplatin       | Randomized, controlled                | 65             | No significant differences compared to control group                                         | [158]      |
|                       | N/A                | Platinum, taxane or others | Meta-analysis                        | 353            | RR (95% CI) of incidence of neuropathy was 0.55 (0.29–1.05).                               | [159]      |
| Glutathione           | 1500 mg/m²         | Oxaliplatin       | Randomized, double-blind, placebo-controlled | 52             | Significant improvements in incidence of ≥ Grade 2 neuropathy and neurophysiological findings compared placebo group | [160]      |
| Calmangafodipir       | 2–10 μmol/kg       | Oxaliplatin       | Randomized, controlled                | 173            | Significant improvements in Leonard scale compared to control group                         | [161]      |
| Pregabalin            | 150–600 mg/kg      | Oxaliplatin       | Randomized, double-blind, placebo-controlled | 199            | No significant differences compared to placebo group in pain score                          | [162]      |
| Minocycline           | 200 mg/day         | Oxaliplatin       | Randomized                            | 66             | No significant differences compared to control group                                         | [163]      |

Abbreviations: 95% CI, 95% confidence interval; FACT/GOG-NTx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; RR, relative risk.
Duloxetine was tested in a randomized, double-blind, placebo-controlled, cross-over trial, for its ability to treat neuropathy in patients with taxane or platinum [148]. In this study, relative risks (RRs) (95% confidence interval (CI)) of experiencing 30% and 50% pain reduction were 1.96 (1.15–3.35) and 2.43 (1.11–5.30), respectively. A sub-analysis of this study indicates that duloxetine is more effective than taxanes in treating platinum-induced neuropathy.

Intravenous injection of calcium and magnesium is thought to chelate oxalate, and the preventive effects for oxaliplatin-induced peripheral neurotoxicity have been investigated since before [149–152]. Some studies reported significant inhibitory effects on oxaliplatin-related neuropathy [149,150], some studies did not confirm significant effects [151,152]. The results of a meta-analysis including five studies showed that calcium and magnesium had no significant effect on neuropathy (relative risks (RRs) (95% CI) of incidence of ≥ Grade 2 neuropathy and ≥ Grade 1 chronic neuropathy were 0.81 (0.60–1.11) and 0.95 (0.69–1.32), respectively.) [153].

Goshajinkigan, a Japanese herbal medicine, has been studied in several clinical trials [154–156]. In a randomized controlled trial, goshajinkigan significantly reduced the incidence of Grade 2 or higher neuropathy [154]. In goshajinkigan oxaliplatin neurotoxicity evaluation (GONE) study, the incidence of Grade 2 or higher neuropathy until the 8th cycle was 39 and 51% in goshajinkigan and placebo groups, respectively, which was not statistically significant [155]. This study concluded that goshajinkigan appears to have an acceptable safety margin and a promising effect in delaying the onset of Grade 2 or greater peripheral neuropathy [155]. However, in the interim analysis of goshajinkigan effect for oxaliplatin neurotoxicity inhibition using mFOLFOX6 regimen (GENIUS) study, a multicenter randomized, double-blind, placebo-controlled trial, goshajinkigan significantly increased the incidence of neuropathy [156].

Alpha-lipoic acid and vitamin E, both of which have antioxidant properties, were also examined in clinical trials for their effects on neuropathy in patients using oxaliplatin [157–159]. However, neither has been reported to significantly improve neuropathy. Beside, glutathione and calmanagafodipir, which also have antioxidant effects, were found to significantly improve neuropathy related oxaliplatin treatment in randomized trials [160,161]. However, the dose of glutathione used in this clinical trial was high (1.5 g/m²), and calmanagafodipir is undergoing Phase III trials and not approved as a drug at this time. Other drugs such as pregabalin, a general-purpose drug for neuropathic pain, and minocycline, a glial attenuator, have also been tested in clinical trials, but no significant inhibitory effects have been reported [162,163].

As described above, few drugs have shown clear therapeutic effects on oxaliplatin-induced peripheral neuropathy in clinical trials. Thus, according to the clinical practice guideline updated by the American Society of Clinical Oncology in 2020, no agents have yet to be recommended for preventing chemotherapy-induced peripheral neuropathy and only duloxetine may be used as a treatment for neuropathy [10].

4. Discussion

Recently, the mechanism of oxaliplatin-induced peripheral neuropathy has been elucidated in basic studies, and many drugs and agents targeting this mechanism have been explored and identified for therapy for oxaliplatin-induced peripheral neuropathy. In particular, many inhibitors of neuropathy targeting oxidative stress, inflammatory response, sodium channel, TRP channel, glutamate nervous system, and monoamine nervous system have been identified as candidates for inhibiting oxaliplatin-induced neuropathy in animal research.

Alternatively, very few drugs have shown the efficacy of oxaliplatin for peripheral neuropathy in clinical trials. The American Society of Clinical Oncology’s clinical practice guideline states that only duloxetine can be used for the treatment of chemotherapy-induced peripheral neuropathy [10]. Since duloxetine has been shown to improve pain in clinical trials [148], its use in patients with pain may be beneficial. However, consideration
should be given to side effects such as drowsiness, headache, and dizziness. Goshajinkigan and glutathione are drugs that have few side effects, thus they can be considered easy to treat in patients. Goshajinkigan has been reported both to have therapeutic effects on oxaliplatin-induced peripheral neuropathy and not to have the effects [154–156]. In an animal study, it has been reported that goshajinkigan does not inhibit the progression of chronic neuropathy, but rather relieves neuropathic symptoms [124]. Therefore, it may be used to relieve symptoms in patients with oxaliplatin-induce neuropathy.

While many drugs have been reported in basic research as having the potential to inhibit the neuropathy by oxaliplatin, few drugs have developed sufficient evidence in clinical studies. The “valley of death” between basic researches and clinical applications is considered caused by many issues, including the difference between clinical symptoms and animal assessment methods, the cost and time of conducting clinical research, safety considerations in clinical application, and the lack of collaboration between basic and clinical researchers. It is important to promote translational research, that is, to bridge basic research to clinical research.

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**Abbreviations**

- 5-HT: Serotonin
- 95% CI: 95% confidence interval
- Akt: protein kinase B
- ATF-3: activating transcription factor 3
- ATP: adenosine triphosphate
- CAT: Catalase
- CaMKII: calmodulin-dependent protein kinase II
- DRG: dorsal root ganglia
- ERK: extracellular signal-regulated kinase
- ETA: endothelin A
- ETB: endothelin B
- FACT/GOG-NTx: Functional Assessment of Cancer Therapy/Gynecologic Group-Neurotoxicity
- GENIUS: goshajinkigan effect for oxaliplatin neurotoxicity inhibition using mFOLFOX6 regimen
- GFAP: glial fibrillary acidic protein
- GLT-1: glutamate transporter 1
- GONE: goshajinkigan oxaliplatin neurotoxicity evaluation
- GPx: glutathione peroxidase
- HCN1: hyperpolarization-activated, cyclic nucleotide-gated cation channel 1
- HCN2: hyperpolarization-activated, cyclic nucleotide-gated cation channel 2
- HIF-1: hypoxia inducible factor 1
- HMGB1: high mobility group box 1
- Iba-1: ionized calcium binding adaptor protein 1
- i.c.v.: intracerebroventricular
- IENF: intra-epidermal nerve fibers
- IL-1β: interleukin-1 beta
- IL-6: interleukin-6
- i.m.: intramuscular
- i.t.: intrathecal
- JSPS: Japan Society for the Promotion of Science
- MAPK14: mitogen-activated protein kinase-14
- MBP: myelin basic protein
MEK1/2: mitogen-activated protein kinase kinases 1 and 2
MMP9/2: matrix metalloproteinase-9 and -2
mTOR: mammalian target of rapamycin
nAChR: nicotinic acetylcholine receptor
NF-κB: nuclear factor kappa-B
NMDA: N-methyl-D-aspartate
OCT2: organic cation transporter 2
OCTN1: organic cation transporter novel type 1
PDE: phosphodiesterase
PKC: protein kinase C
RR: relative risk
SOD: superoxide dismutase
S1P: sphingosine-1-phosphate
TAFI: thrombin-activatable fibrinolysis inhibitor
TNF-α: tumor necrosis factor-α
TREK-1: tandem pore domains in weak rectifying K+ channel (TWIK)-related K+ channel 1
TRPA1: transient receptor potential ankyrin 1
TRPM8: transient receptor potential melastatin 8
TRPV1: transient receptor potential vanilloid 1
VEGF: vascular endothelial growth factor

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