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Review

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

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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 had therapeutic effects on oxaliplatin-induced peripheral neuropathy in these basic studies (Table 1).

Table 1. The therapeutic agents for oxaliplati-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 in IENF density	Antioxidant effect	[17]
	Carvedilol	10 mg/kg	Rats	Mechanical and cold allodynia	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 nervedenegerations	Antioxidant effect (upregulation of glutathione)	[20]
	Dimethyl fumarate	200 mg/kg	Rats	Mechanical allodynia and sciatic nervedenegerations	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	Antioxidant effects (downregulation of SOD, CAT, and GPx), and antiinflamattory 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	[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	Inhibition of nitration and activation of superoxide dismutase in mitochondria, and increase in ATP production in primary nerve sensory axons	[26]
	MnL4 (SOD mimetic compound)	15 mg/kg	Rats	Motor coordination, mechanical and cold allodynia	Antioxidative effects and inactivations of caspase 3/7 in astrocyte	[27]
	Niclosamide	10 mg/kg	Mice	Tactile hypoesthesia and thermal hyperalgesia, IENF density, and demyelination	Antioxidative and antiinflammatory effects	[28]

Table 1. *Cont.*

Therapeutic Targets	Therapeutic Agents	Dose	Animals	Symptoms that Showed Improvement	Mechanisms	References
Oxidative stress	Phosphatidylcholine	300 mg/kg	Rats	Mechanical and thermal allodynia	Antioxidative effects (downregulation of malondialdehyde, glutathione, GPx, and SOD in sciatic nerve) and modulation of microglial activities	[29]
	Quercetin	20 mg/kg	Mice	Mechanical allodynia	Antioxidant effect	[30]
	Quercetin	25–100 mg/kg	Mice	Mechanical and cold allodynia	Downregulation of nitric oxide and peroxynitrite	[31]
	Resveratrol	100 mg/kg	Mice	Mechanical allodynia	Antioxidant effect	[30]
	Rosiglitazone	3–10 mg/kg	Rats	Mechanical, cold allodynia and motor coordination	Prevention of catalase impairment	[32]
	Rosmarinic Acid	25–50 mg/kg	Rats	Mechanical and cold allodynia	Reduction of oxidative stress, improvement of mitochondrial function, inhibition of spinal glial cell activation, and suppression of expression of inflammatory markers	[33]
	Rutin	20 mg/kg	Mice	Mechanical allodynia	Antioxidant effect	[30]
	Rutin	25–100 mg/kg	Mice	Mechanical and cold allodynia	Downregulation of nitric oxide and peroxynitrite	[31]
	Silibinin	100 mg/kg	Rats	Mechanical and cold allodynia	Improvement of oxidative alterations	[34]
	SS-20 (mitochondria-targeted peptide)	5–10 mg/kg	Mice	Mechanical allodynia and IENF density	Mitochondrial protection	[35]
	SS-31	5 mg/kg	Mice	Mechanical and cold allodynia	Mitochondria-targeted antioxidant	[36]
	Sulforaphane	5 mg/kg	Mice	Mechanical allodynia and morphological alterations, mitochondrial dysfunction in DRG	Activation of the Nrf2 signaling pathway	[37]
	Vitamin C	50–100 mg/kg	Rats	Mechanical, thermal and cold allodynia	Antioxidant effect	[15]
	Vitis vinifera extract	300 mg/kg	Rats	Mechanical and cold allodynia	Antioxidant effect	[38]
	α-tocopherol	100 mg/kg	Rats	Mechanical and cold allodynia	Improvement of oxidative alterations	[34]

Table 1. *Cont.*

Therapeutic Targets	Therapeutic Agents	Dose	Animals	Symptoms that Showed Improvement	Mechanisms	References
Inflammatory	Bee Venom derived phospholipase A_2	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]
K channel	Glucosinolate glucoraphanin	4.43–119.79 μmol/kg	Mice	Mechanical allodynia	Releasing H_2S and modulating Kv_7 channels	[50]
	Isothiocyanate sulforaphane	1.33–13.31 μmol/kg	Mice	Mechanical allodynia	Releasing H_2S and modulating Kv_7 channels	[50]
	Allyl-isothiocyanate	1.33–13.31 μmol/kg	Mice	Cold allodynia	Releasing H_2S and modulating Kv_7 channels	[51]
	Phenyl- and carboxyphenyl-isothiocyanate	1.33–13.31 μmol/kg	Mice	Cold allodynia	Releasing H_2S and modulating Kv_7 channels	[51]
	Riluzole	7.5 mg/kg	Mice	Mechanical and cold allodynia	Involvement of TREK-1 potassium channel	[52]
Ca channel	Gabapentin	10–100 mg/kg	Mice	Mechanical allodynia	Attenuation of cofilin phosphorylation in spinal cord	[53]
	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	*N/A*	[54]

Table 1. *Cont.*

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	Mechanical and 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	HCN1 inhibitor	[61]
	MEL55A	30 mg/kg	Mice	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]
Glutamate	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	Thermal hyperalgesia	Glutamate carboxypeptidase II inhibitor	[66]
	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]

Table 1. *Cont.*

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]
Endothelin receptor	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]
Cannabinoid receptor	Cannabidiol	1.25–10 mg/kg	Mice	Mechanical allodynia	*N/A*	[75]
Sigma-1 receptor	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]
Opioid receptor	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]
Monoamines	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 α_2-adrenegic receptors	[82]
	Bee venom acupuncture	0.25–2.5 mg/kg	Mice	Mechanical and cold allodynia	Activations of spinal opioidergic and 5-HT_3 receptors	[83]
	Bee venom acupuncture	0.25–1 mg/kg	Rats	Cold allodynia	Activation of the noradrenergic system	[84]
	Bee Venom derived phospholipase A_2	0.2 mg/kg	Mice	Mechanical and cold allodynia	Activation of the noradrenergic system, via α_2-adrenegic receptors	[85]
	Clomipramine	2.5 mg/kg	Rats	Cold allodynia	*N/A*	[11]
	Clonidine	0.1 mg/kg	Mice	Mechanical allodynia and spinal p-p38 MAPK expression	α_2 adrenoceptor agonist	[86]
	Duloxetine	30–60 mg/kg	Mice	Mechanical and cold allodynia	Activating spinal α_1-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-HT_{2C} receptor	[89]
	Melittin (major content of bee venom)	0.5 mg/kg	Mice	Mechanical and cold allodynia	Activating the spinal α_1- and α_2-adrenergic receptors.	[90]
	Morphine	2–5 mg/kg	Mice	Mechanical and cold allodynia	Activations of spinal opioidergic and 5-HT_4 receptors	[83]

Table 1. *Cont.*

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_{1A} 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_2-adrenoceptor	[92]
	Tandospirone	1–3 mg/kg	Mice	Mechanical allodynia and mast cell migration	5-HT_{1A} 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_{1A} receptor agonist	[93]
Acetylcholine receptor	Citicoline (cytidine-5′-diphosphate- choline; CDP-choline)	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]
	αO-Conotoxin GeXIVA 1,2	32–128 mg/kg	Rats	Mechanical and cold allodynia	Antagonism of the α9α10 nAChR	[97]
	α-conotoxin RgIA	2–10 nmol (i.m.)	Rats	Mechanical, cold allodynia, and morphological changes of DRG	α9α10 nAChR antagonist	[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]
Orexin receptor	Orexin-A	0.1–1 nmol (i.c.v.)	Mice	Mechanical allodynia	Orexin type-1 receptor agonist	[101]
Histamine receptor	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]

Table 1. *Cont.*

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 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	Motor dysfunction and electrophysiological assesment of motor nerves	*N/A*	[110]
	Alogliptin	10 mg/kg	Rats	Mechanical allodynia and sciatic nervedenegerations	Neuroprotective effects	[111]
Others	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]
	Aqueous extract of Lithospermi Radix	250 mg/kg	Mice	Mechanical allodynia	Attenuation of spinal microglia and astrocyte	[114]
	Aripiprazole	10 mg/kg	Mice	Mechanical allodynia	*N/A*	[115]
	Astragali radix	100–300 mg/kg	Rats	Mechanical and thermal allodynia	Reductions of morphometric and molecular alterations in peripheral nerve and DRG, and inactivation of microglia and astrocytes in spinal cord and brain	[116]
	Benztropine	10 mg/kg	Mice	Mecahnical, cold allodynia, and demyelination in sciatic nerve	*N/A*	[117]
	Ceftriaxone	200 mg/kg	Mice	Mechanical allodynia	*N/A*	[115]

Table 1. *Cont.*

Therapeutic Targets	Therapeutic Agents	Dose	Animals	Symptoms that Showed Improvement	Mechanisms	References
Others	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	Mecahnical, cold allodynia, and demyelination in sciatic nerve	Neuroprotective effects	[121]
	Fulvestrant	5–10 mg/kg	Rats	Mechanical allodynia and sciatic nervedenegerations	Neuroprotective effects	[122]
	Goshajinkigan	300–1000 mg/kg	Mice	Mechanical and cold allodynia	*N/A*	[123]
	Goshajinkigan	300–1000 mg/kg	Rats	Mechanical and cold allodynia	*N/A*	[124]
	Hirudin	10 mg/kg	Mice	Mechanical allodynia	Downregulation of p38, HIF-1α and MMP-9/2	[125]
	HM01	10–30 mg/kg	Rats	Nerveconductionvelocity of digital nerve, caudal nerve and IENF density	Ghrelin agonist	[126]
	Melatonin	3–10 mg/kg	Mice	Mechanical and cold allodynia	Antioxidant effect, improvement of mitochondrial function, activation of autophagy pathway, and anti-apoptotic effect	[127]
	Metformin	250 mg/kg	Rats	Mecahnical, cold allodynia, decrease in IENF density, and increase in GFAP of spinal cord	*N/A*	[128]
	Metformin	250 mg/kg	Mice	Mechanical allodynia	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 allodynia	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 allodynia	Neuroprotective effects	[131]

Table 1. *Cont.*

Therapeutic Targets	Therapeutic Agents	Dose	Animals	Symptoms that Showed Improvement	Mechanisms	References
Others	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 root extract (Danshen)	300–600 mg/kg	Mice	Cold allodynia	*N/A*	[119]
	Tanshinone IIA	25 mg/kg	Rats	Mecahnical, 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, dischange in nerve sensory conduction velocity, caudal nerve fibers density, and IENF density	*N/A*	[137]
	Water extract of Lepidium meyenii 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; 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; 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; PI3K, 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, phenyl-isothiocyanate 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 [55–60].

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 overexpression, 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.

Table 2. The therapeutic drugs for oxaliplati-induced peripheral neuropathy in clinical experiments.

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 and magnesium	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, or pre-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]
Goshajinkigan	*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]
	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	No significant differences compared to control group RR (95% CI) of incidence of neuropathy was 0.55 (0.29–1.05).	[159]
Glutathione	1500 mg/m^2	Oxaliplatin	Randomized, double-blind, placebo-controlled	52	Significant improvements in incidence of $\geq$ 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 calmangafordipir, 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/m^2), and calmangafodipir 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
PI3K	phosphatidylinositol-3 kinase
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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