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ORIGINAL RESEARCH

Interventional Clinical Trials on Diabetic Peripheral Neuropathy: A Retrospective Analysis

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Aims/Introduction: Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes. At present, there is no comprehensive summary of the clinical trials related to DPN. In this article, we summarized the basic characteristics of the interventional clinical trials pertaining to DPN to determine the current status of research in this field and the existing issues.

Materials and Methods: We searched the World Health Organization International Clinical Trial Registration Platform (ICTRP), PubMed and Web of Science for clinical trials from 2005 to April 2021 and extracted 149 registered and 459 published clinical trials on DPN. We summarized the characteristics of the clinical trials, including the source registration, recruitment status, stage, age group, allocation method, intervention, end point classification, funding source, and treatment.

Results: After excluding noninterventional and nontreatment trials, 149 registered clinical trials out of 292 records from 12 registration centers and 459 published articles were included in this study. Among the registered trials, 43% had been completed, and 34.4% had been published in peer-reviewed journals. Among these trials, more than half used random allocation and blinded placebo-controlled methodologies. A total of 40.3% of the trials were multicenter studies, 63.8% of the treatments were drug therapies, and the endpoint classifications of 49% were efficacy and safety. Of the 459 published interventional clinical trials on DPN, 69.7% of the trials used drug treatments; more than half were randomized, double-blind, placebo-controlled clinical trials; 94.1% had positive outcomes; 46.4% had a target size of 50; and 22.9% were multicenter.

Conclusion: This paper systematically summarizes the current status of interventional trials on DPN registered in the ICTRP and published clinical trials and provides a reference for the development of high-quality intervention strategies for DPN in the future.

Keywords: diabetic peripheral neuropathy, clinical interventional trials, ICTRP, clinical characteristics

Introduction

According to the International Diabetes Federation (IDF), the global prevalence of diabetes will rise to 578 million by 2030 and 700 million by 2045.[1] Diabetic peripheral neuropathy (DPN) is the most common microvascular complication of diabetes,[2] and 50% of diabetic patients eventually develop neuropathy during the course of their illness.[3] DPN is defined as symptoms of peripheral nerve dysfunction after other reasons are excluded.[4] Patients with DPN usually have numbness, tingling, pain or weakness that starts at the distal ends of the limbs, with the characteristic stocking-glove distribution, and progresses to the

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proximal ends.[5] Many DPN patients suffer from chronic and severe neuropathic pain, which is difficult to treat and manage, seriously influencing their quality of life, imposing a heavy burden on them and increasing their medical costs.[6] Currently, the treatment for DPN relies on prevention, blood sugar control, and pain and symptom control.[7] Many patients do not receive effective treatment methods, and drug therapy is still the main treatment for DPN.[8,9] The lack of efficacy and the occurrence of side effects of the drugs currently used for the prevention and treatment of DPN are serious clinical problems, and there is an urgent need to conduct in-depth research to develop new strategies.[10]

Clinical trials are pivotal in evaluating the efficacy of novel interventional therapies for different diseases.[11] It is necessary to summarize the current status of clinical trials on DPN to improve awareness among researchers and doctors and promote current and future therapies and interventions. The World Health Organization (WHO) International Clinical Trials Registration Platform (ICTRP: http://www.who.int/ictrp) is a global database that aims to make information regarding all clinical trials involving human beings publicly available.[12] At present, there is no summary of the clinical studies on DPN registered in the ICTRP. We systematically summarized the characteristics of ongoing and completed interventional clinical trials on DPN with the aim of determining their current status and future research directions.

Materials and Methods

Data Source and Search Strategy

The preparation for this study occurred in three steps: (1) we obtained the registration records of clinical trials on DPN as of December 2020 in the WHO ICTRP Search Portal (http://apps.who.int/trialsearch) using the term "diabetic peripheral neuropathy"; (2) two investigators (MW and ZZ) used standardized strategies to manually search for peer-reviewed publications of completed clinical trials that involved searching for the publication in the ICTRP database, followed by searching in PubMed and Google Scholar using the NCT number or the short title of the trial and the name of the main researcher if the publication was not confirmed; and (3) the investigators reviewed the published clinical trials according to the preferred items for reporting systematic reviews and meta-analyses (PRISMA) guidelines.[13] The databases were searched from the database inception to December 2020, and the language of publication was limited to English in PubMed and the Web of Science.

Data Extraction and Selection

All registered clinical trials were included regardless of language. The retrieved records from the ICTRP were exported to Microsoft Excel for filtering by title, abstract, and availability of the full-text article from March 31, 2005, to April 20, 2021 to exclude clinical trials on topics other than DPN. Then, we conducted an advanced search using the terms "diabetic peripheral neuropathy" and

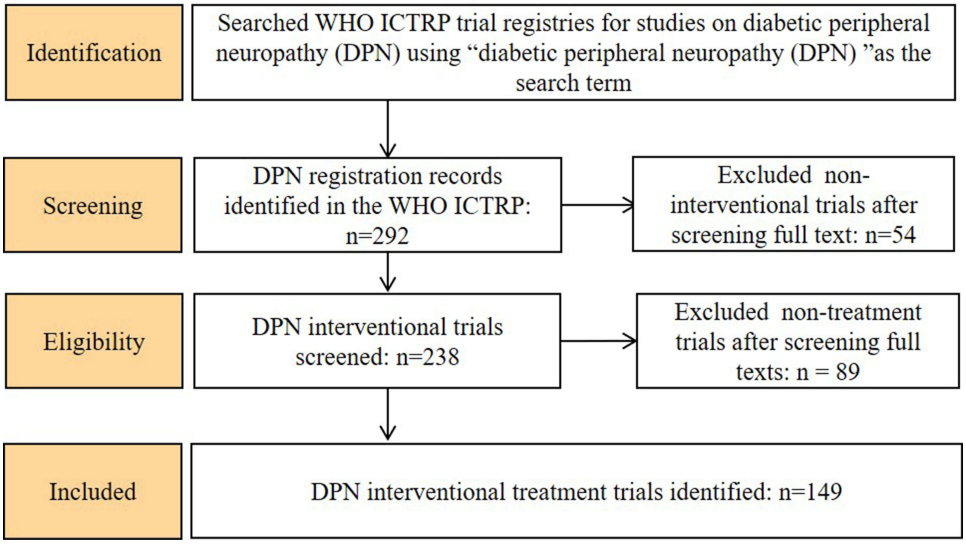

Figure 1 Flowchart of clinical trial selection from the WHO International Clinical Trials Registry Platform (ICTRP).

"intervention" to obtain interventional or treatment trials on DPN for further analysis. Interventional clinical trials on DPN were identified and confirmed. Noninterventional or nontreatment trials were excluded after screening the full-text articles. The following data were extracted from the clinical trial records in the ICTRP database and entered into Excel: source register, recruitment status, trial phase, eligibility criteria (age group and sex), allocation, intervention model, number of arms, endpoint classification, placebo comparator, participating center, masking style, target size, treatment, condition, primary outcome, and secondary outcome. The type of funding for the clinical trials, such as whether the trials were funded by industry, was determined by the identification of the primary funding source. Before the data were extracted, the original registration website was visited to ensure that the data were current. The primary and secondary outcomes were classified and analyzed according to the items listed on the original website, and those that could not be classified were listed as "other". The publication was confirmed by matching the research characteristics outlined in the ICTRP database with the corresponding descriptions in the published manuscript. If multiple publications pertained to the same registered trial, the first article to report the main results was selected, and the others were excluded. We performed a systematic literature review and searched for published clinical trials on DPN from the date of the inception of the database to April 2021, excluding unlisted and unrelated studies. The first author (MW) used a predefined form to extract the following data, which were then entered into Microsoft Excel: title, year of publication, intervention duration (weeks), sample size, treatment, masking/blinding, randomized controlled trial design, placebo comparator, participating center and outcome.

Discrepancies

The data analysis was conducted by two researchers (MW, ZZ), and any differences between the two researchers were resolved. If the two researchers could not reach an agreement, the final decision was made by a third researcher (XL).

Statistical Analyses

Missing values were excluded from the analysis unless otherwise indicated. Descriptive statistics were used to describe the characteristics of the clinical trials. Categorical variables are expressed as frequencies and percentages. SAS software was used for all statistical analyses (version 9.3, SAS Institute Inc., Cary, NC, USA). GraphPad Prism 8.2.1 (GraphPad Software, San Diego, CA, USA) was used to construct the histograms and pie charts.

Results

Basic Characteristics of Interventional Clinical Trials on DPN

A total of 292 registered records of interventional clinical trials on DPN were retrieved from the ICTRP. Among these trials, 54 noninterventional trials were excluded: 50

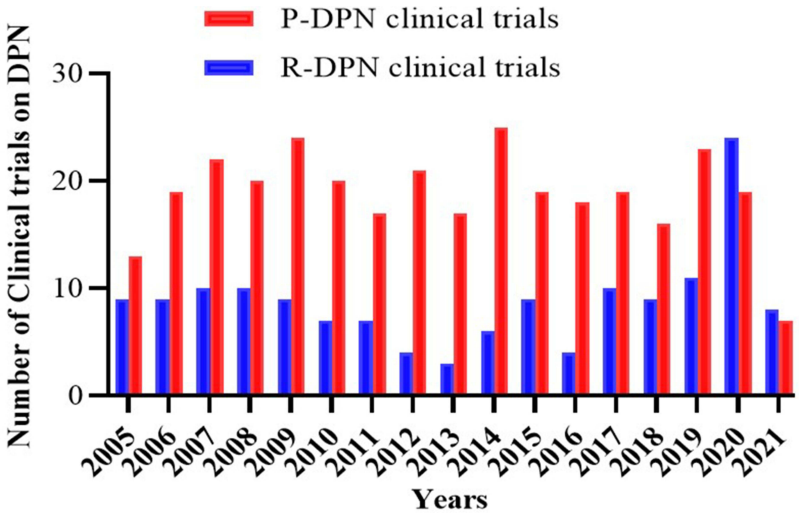

Figure 2 Number of clinical trials on DPN registered and published between 2005 and December 2020. R-clinical trials on DPN: registered clinical trials on DPN; P-clinical trials on DPN: published clinical trials on DPN.

Table 1 Characteristics of Interventional Clinical Trials on DPN Registered in the ICTRP

Characteristics	Category	N=149	Percentage of Records (%)
Source register	ANZCTR	5	3.4
	ClinicalTrials.gov	112	75.2
	CRIS	1	0.7
	IRCT	7	4.7
	ISRCTN	3	2.0
	JPRN	5	3.4
	PACTR	2	1.3
	REBEC	1	0.7
	ChiCTR	4	2.7
	CTRI	3	2.0
	EUCTR	1	0.7
	TCTR	5	3.4
Recruitment status	Completed	74	49.7
	Recruiting	25	16.8
	Not recruiting	29	19.5
	Terminated	10	6.7
	Withdrawn	5	3.4
	Unknown/Missing	6	4.0
Target size	0 to 50	47	31.5
	51 to 100	24	16.1
	101 to 200	30	20.1
	201 to 500	41	27.5
	501 to 1000	6	4.0
	Unknown/Missing	1	0.7
Participating center	Multicenter	60	40.3
	Single center	87	58.4
	Unknown/Missing	2	1.3
Age group	Child/Adult/Senior	2	1.3
	Adult	15	10.1
	Adult/Senior	130	87.2
	Unknown/Missing	2	1.3
Allocation	Randomized	116	77.9
	Non-randomized	17	11.4
	Unknown/Missing	16	10.7
Number of arms	1	23	15.4
	2	84	56.4
	3	18	12.1
	4	9	6.0
	≥5	9	6.0
	Unknown/Missing	6	4.0
Masking/Blinding	Single blind	8	5.4
	Double blind	41	27.5
	Quadruple blind	29	19.5
	Triple blind	17	11.4
	Open label	43	28.9
	Unknown/Missing	11	7.4
Treatments	Symptomatic treatment of DPN	51	34.2
	Pathogenetic treatment	26	17.4
	Other pharmacologic agents	18	12.1
	Device	25	16.8
	Exercise	9	6.0
	Medical food	2	1.3
	Genetic/Biological therapy	8	5.4
	Massage/ Acupuncture	6	4.0
	Revascularization	1	0.7
	Hyperbaric Oxygen Therapy	1	0.7
	Lifestyle Modification Program	2	1.3
Condition	Diabetic peripheral neuropathy	94	63.1
	Painful diabetic neuropathy	55	36.9
Phase	Phase I/Phase I-Phase II	11	7.4
	Phase II	46	30.9
	Phase II-Phase III	4	2.7
	Phase III	23	15.4
	Phase IV	17	11.4
	Unknown/Missing	48	32.2
Intervention model	Parallel assignment	107	71.8
	Crossover assignment	10	6.7
	Sequential assignment	2	1.3
	Single group assignment	19	12.8
	Unknown/Missing	11	7.4
Endpoint classification	Efficacy	52	34.9
	Efficacy and safety	73	49.0
	Efficacy, safety and pharmacokinetics	3	2.0
	Others	21	14.1
Placebo comparator	Yes	65	43.6
	No	77	51.7
	Unknown/Missing	11	7.4

Table 1 (Continued).

Characteristics	Category	N=149	Percentage of Records (%)
	Unknown/Missing	7	4.7
Funding source	Industry	80	53.7
	Non-industry	69	46.3
Results of completed trials	Results available	32	21.5
	No results available	117	78.5
Primary completed trials	Yes	64	43.0
	No	85	57.0
Publication[a]	Published	22	29.7
	Not published	52	70.3
Location	North America	76	51.0
	Europe	27	18.1
	Asia	31	20.8
	South America	4	2.7
	Africa	9	6.0
	Latin America	2	1.3

Note: [a]The total is the publication rate of completed trials.

observational trials, three factorial trials, and one diagnostic test trial. After screening the full texts of the remaining studies, 89 nontreatment trials were excluded, including 13 trials on supportive care, 67 trials with unknown/missing information, and nine other trials. Finally, 149 records of interventional clinical trials on DPN were included for further analysis (Figure 1). As shown in Figure 2, we found that these 149 trials were registered from 2005 to 2021, with approximately ten registrations every year. In 2020, the number of interventional clinical trials on DPN was two times that in the previous year. We found that Clinicaltrials.gov had the largest number and earliest submissions of interventional clinical trials on DPN, and all other registration platforms had fewer than 10 trials (Figure 2, Table 1).

With regard to recruitment, we found that 49.7% of the trials had completed recruitment. Approximately 68% of the clinical trials had a target size of fewer than 200, 31.5% of which had a sample size of less than 50. More than half of the trials were single-center studies, and approximately 87.2% of the trials focused on adults/elderly people. Most trials were randomized (77.9%) and blinded (63.7%), but approximately 51.7% of the trials did not use a placebo as a control. Trials in Phase II accounted for 30.9% of the total. Approximately 71.8% of the intervention models were parallel assignments. Drugs (63.8%) were the most common interventional treatment, followed by devices (16.8%). The endpoint classification in 49% of the trials was "efficacy and safety", followed by efficacy alone in 34.9%; however, 78.5% of the trials had no available results. The most common funding source was industry (53.7%), and nearly 51% of the trials were conducted in North America.

Interventional Characteristics of 149 Clinical Trials on DPN

Based on our analysis, there were nine types of interventions for the treatment of patients with DPN: drugs; devices; exercise; medical foods; genetic/biological therapies; revascularization; hyperbaric oxygen therapy; lifestyle modification programs; and massage/acupuncture. Of the 149 trials, three-fifths focused on drug interventions, followed by 19.4% focusing on supplementary alternative therapies and 16.8% focusing on devices, as shown in Figure 3A. In the 95 trials on drug therapies, 34.2% involved the symptomatic treatment of DPN; 17.5% involved pathogenetic treatments of DPN, and 12.2% were on other pharmacologic agents. These drugs included antidepressants, anticonvulsants, topical medications, opioid analgesics, nonopioid painkillers, vitamins and their derivatives, ion channel drugs, and traditional Chinese medicine (Figure 3B).

Anticonvulsant drugs, such as pregabalin, gabapentin, carbamazepine, and pregabalin, are most commonly used for the treatment of DPN. Moreover, some new drugs have emerged, such as the new nonopioid analgesic drugs SKL11197, SR419, and LX9211. In addition, clinical trials were performed to investigate the effects of certain drugs on the nourishment of nerves, such as vitamins and their derivatives, caper extracts, and green tea extracts. As shown in Figures 3C, 25 device intervention trials included management/therapy systems (3), wearable aids (3), laser treatments (4), electrical stimulation (13), peristaltic pulse pneumatic compression devices (1), and extracorporeal shock wave therapy (1). Among the 25 trials on devices, electrical stimulation as an auxiliary treatment measure accounted for half. An overview of these interventions in the 149 clinical trials on DPN is shown in Table 2 and Figure 3.

Primary and secondary outcomes were used to directly reflect the objectives of the clinical trials and assess the

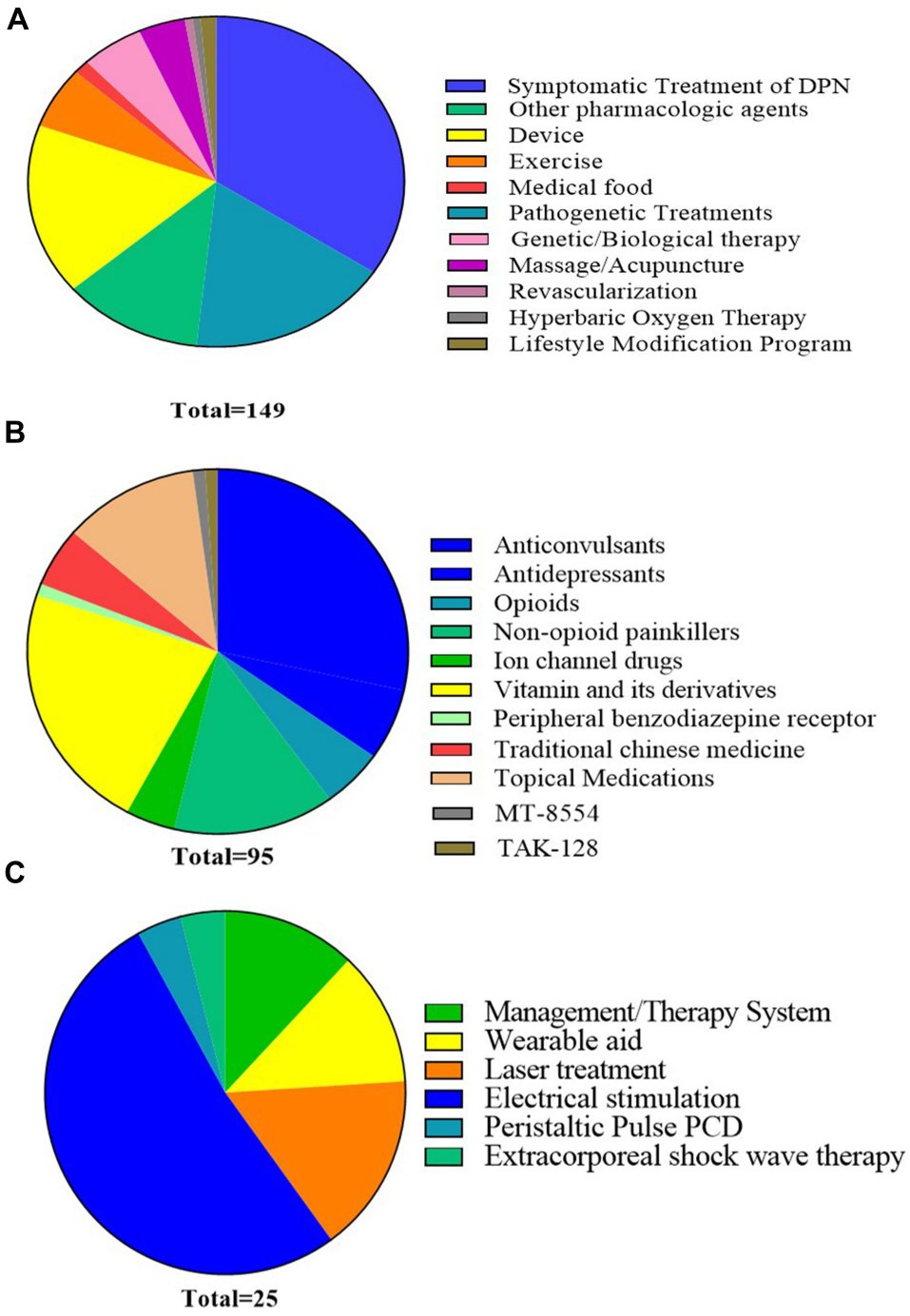

Figure 3 Overview of the interventions in 149 clinical trials on DPN. (**A**) Intervention categories of 149 clinical trials on DPN; (**B**) Drug interventions in 92 clinical trials on DPN; (**C**) Device interventions in 25 clinical trials on DPN.

efficacy of the intervention or drug treatment.[14] We summarized the primary and secondary outcomes of the 149 interventional clinical trials and found 313 primary outcomes and 725 secondary outcomes. The evolution of DPN pain was the most common evaluation index, accounting for 31.9% of the primary outcomes and 22.3% of the secondary outcomes. Among the primary outcomes, clinical symptoms or signs accounted for 16.9%, and neurophysiology accounted for 13.1%. The categories and percentages of the primary outcomes and secondary outcomes in the 149 interventional trials are listed in Table 3.

Table 2 Overview of the Interventions from 149 Clinical Trials on DPN

Interventional Categories	N=149	Percentage of Records (%)
Symptomatic Treatment of DPN		
Anticonvulsants	27	18.1
Antidepressants	6	4.0
Opioids	5	3.4
Non-opioid painkillers	13	8.7
Pathogenetic Treatments		
Ion channel drugs	4	2.7
Vitamin and its derivatives	21	14.1
Peripheral benzodiazepine receptor (PBR)	1	0.7
Other Pharmacologic Agents		
Traditional Chinese medicine	5	3.4
Topical medications	11	7.4
MT-8554	1	0.7
TAK-128	1	0.7
Device		
Management/Therapy system	3	2.0
Wearable aid	3	2.0
Laser treatment	4	2.7
Electrical stimulation	13	8.7
Peristaltic pulse pneumatic compression device	1	0.7
Extracorporeal shock wave therapy	1	0.7
Exercise	9	6.0
Medical food	2	1.3
Genetic/Biological therapy	8	5.4
Massage/Acupuncture	6	4.0
Revascularization	1	0.7
Hyperbaric oxygen therapy	1	0.7
Lifestyle modification program	2	1.3

Table 3 Primary Outcomes and Secondary Outcomes of 149 Interventional Trials on DPN

Outcomes	N	Percentage of Records (%)
Primary outcomes (N=313)		
Physical examinations	11	3.5
Risk of falls	17	5.4
Evaluation of diabetic peripheral neuropathic pain	100	31.9
Neurophysiology	41	13.1
Clinical symptoms or signs	53	16.9
Safety/Tolerability/Efficacy	13	4.2
Pharmacokinetics	7	2.2
Laboratory tests	26	8.3
Epidermal nerve fiber density	6	1.9
Adverse events	10	3.2
Others	29	9.3
Secondary outcomes (N=725)		
Physical examinations	10	1.4
Evaluation of diabetic peripheral neuropathic pain	162	22.3
Laboratory tests	98	13.5
Quality of life	69	9.5
Depression/anxiety score	24	3.3
Clinical symptoms or signs	77	10.6
Neurophysiology	38	5.2
Sleep interference score	51	7.0
Patient/Clinician evaluation	39	5.4
Risk of falls	18	2.5
Usage of rescue medication/Rescue pain medication use	12	1.7
Adverse events	12	1.7
Safety/Efficacy/Tolerability	12	1.7
Corneal confocal microscopy	1	0.1
Others	102	14.1

Characteristics of Interventional Trials According to Publication Status

As of December 2020, 74 clinical trials on DPN had been completed. We found that only 29.7% of the trial outcomes were published in peer-reviewed journals, and 70.3% of the trial outcomes were unpublished. Drugs (81.8%) were the most common interventional treatment in the published trials; among them, symptomatic treatment of DPN was used in 68.2% of trials, pathogenetic treatments in 13.6% and device treatment in 18.2%. More than 81.8% of the published trials used a random allocation method, and 54.5% of the published trials used masking and a placebo comparator. All trials reported positive outcomes. Approximately 40.9% of the trials had an intervention duration of 8–12 weeks. In total, 50% of published trials had a large sample size. Approximately 90.9% of the published trials were funded by industry sources, and 86.4% of the trials were multicenter studies. Multicenter trials increase the level of evidence and provide relatively more reliable conclusions (Table 4).

Table 4 Characteristics of Interventional Trials According to Publication Status

Interventional Categories	Published (N=22)	Percentage of Records (%)
Treatment		
Symptomatic	15	68.2
Treatment of DPN		
Pathogenetic	3	13.6
Treatments		
Device	4	18.2
Allocation		
Randomized	18	81.8
Non-randomized	4	18.2
Masking/Blinding		
Single blind	1	4.5
Double blind	4	18.2
Quadruple blind	4	18.2
Triple blind	3	13.6
Open label	10	45.5
Placebo comparator		
Yes	12	54.5
No	10	45.5
Outcome		
Positive	22	100.0
Intervention time (Weeks)		
≤0 to ≤4	3	13.6
>4 to ≤8	3	13.6
>8 to ≤12	9	40.9
>12 to ≤16	4	18.2
>16	3	13.6
Target size		
0 to 50	7	31.8
51 to 100	1	4.5
101 to 200	3	13.6
201 to 500	9	40.9
501 to 1000	2	9.1
Funding source		
Industry	20	90.9
Non-industry	2	9.1
Participating center		
Multicenter	19	86.4
Single center	3	13.6

Characteristics of Published Clinical Trials on DPN

Because many registered trials do not update their results in a timely manner, we searched the published clinical trials to determine the progress that has been made in the field of DPN research. From 2005 to 2021, approximately 20 articles on clinical trials pertaining to DPN were published annually (Figure 2). We retrieved 2534 records of clinical trials on DN from the PubMed and Web of Science databases. We excluded 333 records not included in the databases, 202 duplicates, and 1540 irrelevant records. The final records were articles on pathogenesis and epidemiology (141), screening and diagnosis (137), diabetes mellitus and complications (646), peripheral neuralgia (243), diabetic foot (147), pharmacokinetics (5), noninterventional treatments (46), reviews (83), animal or in vitro studies (30), and other topics (62). Finally, 459 articles were included in the analysis (Figures 2 and 4).

Similar to the results of the analysis of registered clinical trials, the main interventions in the published articles were drugs, and more than half of the clinical trial designs were randomized, double-blind, and placebo controlled. The intervention time period was evenly distributed, but only 4.6% of the studies had an intervention duration lasting 12–16 weeks. In total, 46.4% of the studies had target sizes smaller than 50, and 77.1% of the articles reported single-center studies. Of the drug-related interventional trials, 28.5% focused on symptomatic treatment of DPN, and 18.1% focused on pathogenetic treatments. Among the device-related interventional trials, 58.5% investigated electrical stimulation. Peripheral nerve pain was used as the evaluation criterion (Tables 5 and 6, Figures 5 and 6).

Discussion

Through the ICTRP search portal, we identified recent clinical trials on DPN and completed the first summary and extensive investigation of the 149 registered clinical trials on DPN from 12 registries. Half of the clinical trials involving adult/senior patients did not use placebo, were conducted in a single center and were supported by industry funding. Most of the trials had small sample sizes (<200), used parallel interventions and investigated different drugs. However, only approximately 22% of trials have available results, and 30% of those trials have published the results in a peer-reviewed publication.

Comprehensively analyzing the status of clinical trials on DPN is difficult if the ICTRP platform is not updated in a timely manner. Therefore, we searched

clinical trials on DPN published in the PubMed and Web of Science databases. We found that the published clinical trials on DPN have the same characteristics as the registered clinical trials on DPN, but there are insufficient clinical trials on DPN, with approximately ten trials registered each year and approximately twenty articles published each year. We found that 6% of published interventional clinical trials on DPN reported negative results, which may be related to the small dose of the drug or the short duration of action, the selected subjects, and the complicated etiology of DPN. Therefore, a comprehensive clinical trial scheme for DPN is needed to provide a reference for future clinical research.

In this study, the target size of most registered and published clinical trials on DPN was less than 50, which may be related to the large proportion of Phase I to Phase II study trials among the registered trials. In studies involving vulnerable and underrepresented populations, early studies, and trials on rare diseases, a small sample size is reasonable.[15,16] However, in most trials, a sample size that is too small will lead to inaccurate estimates in descriptive studies and inaccurate representations of statistical significance in analytical or comparative studies.[17,18] Some drugs and treatments require a large sample size for investigation and verification.[19–21] Therefore, it is necessary to include a large sample size to estimate the reliability and validity. In addition, single-center studies were common, and half of the clinical trials were concentrated in North America. Although the homogeneity of the samples is thereby ensured, these trials cannot meet the diversity and capacity requirements, cannot meet the regulatory requirements in multiple regions and do not reflect the clinical experience in different locations.[22] Therefore, multicenter research can avoid the limitations of single research, and the conclusions can have wider generalizability and greater credibility.[23]

Our study found that 30% of clinical trials on DPN have been published in peer-reviewed journals, and more than half of these trials were randomized, blinded, placebo-controlled, and multicenter studies. Moreover, all published clinical trials reported positive results, which provides a scientific basis for the development of future clinical trials on DPN. However, 70% of the trials are still unpublished. The reasons they remain unpublished may be time constraints, resource limitations, rejection by journals, or bias against publishing negative results. These are important reasons for the low publication rate. Failure to publish is improper scientific

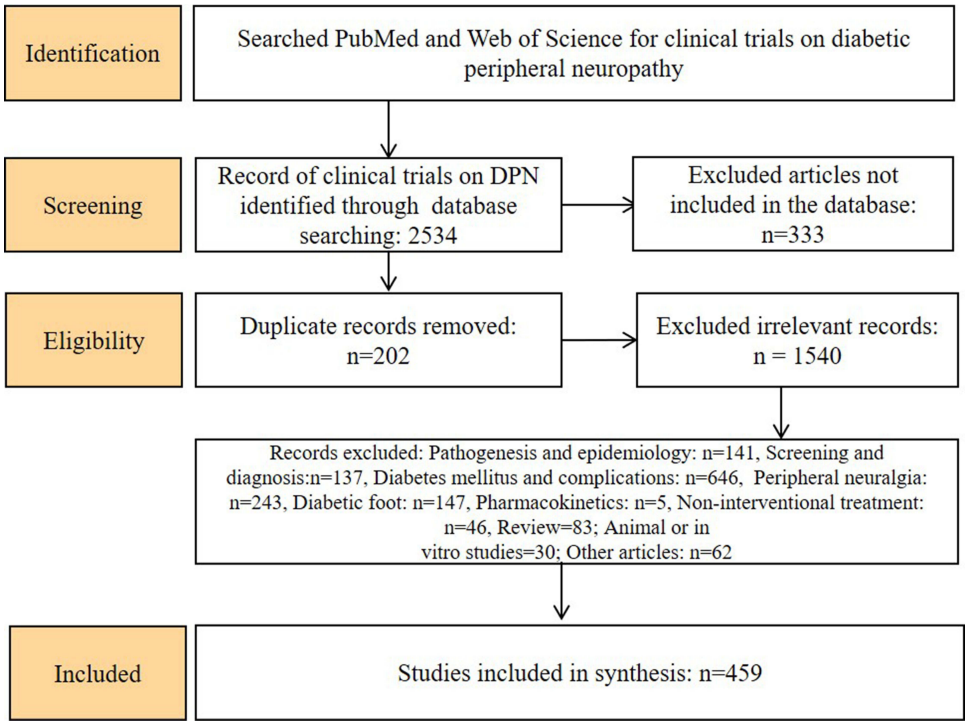

Figure 4 Flowchart of published clinical trial selection.

Table 5 Characteristics of Published Interventional Clinical Trials on DPN

Characteristics	Category	N=459	Percentage of Records (%)
Annual Number of Articles Published	**Years**		
	<2005	140	30.5
	2005	13	2.8
	2006	19	4.1
	2007	22	4.8
	2008	20	4.4
	2009	24	5.2
	2010	20	4.4
	2011	17	3.7
	2012	21	4.6
	2013	17	3.7
	2014	25	5.4
	2015	19	4.1
	2016	18	3.9
	2017	19	4.1
	2018	16	3.5
	2019	23	5.0
	2020	19	4.1
	2021	7	1.5
Treatments			
	Symptomatic treatment of DPN	131	28.5
	Pathogenetic treatments	83	18.1
	Other pharmacologic agents	106	23.1
	Device	53	11.5
	Exercise	40	8.7
	Medical food	5	1.1
	Massage/ Acupuncture	24	5.2
	Genetic/ Biological therapy	17	3.7
Allocation			
	Randomized	323	70.4
	Non-randomized	136	29.6
Masking/Blinding			
	Yes	272	59.3
	No	187	40.7
Placebo comparator			
	Yes	253	55.1
	No	206	44.9
Outcome			
	Negative	27	5.9
	Positive	432	94.1
Intervention time (Weeks)			
	0 to ≤4	131	28.5
	>4 to ≤8	82	17.9
	>8 to ≤12	102	22.2
	>12to ≤16	21	4.6
	>16	123	26.8
Target size			
	0 to 50	213	46.4
	51 to 100	102	22.2
	101 to 200	48	10.5
	201 to 500	64	13.9
	501 to 1000	19	4.1
	>1000	13	2.8
Participating center			
	Multicenter	105	22.9
	Single center	354	77.1

behavior, as unpublished evidence is not available as a reference for the scientific community and clinicians.[24] Therefore, the results of completed trials should be actively published, ensuring that they can serve as a reference for future clinical trials and thereby avoiding wasting resources by unnecessarily repeating research.

Neuropathic pain affects approximately one-third of patients with diabetes,[25,26] and DPN is a key factor in the development of diabetic foot ulcers, the most common cause of amputation.[14] With the discovery of risk factors for DPN and a deepening understanding of the pathogenesis,[27] many researchers have developed effective treatments for DPN. Clinical trials have focused on various treatment strategies for specific pathogeneses of DPN. However, the treatment methods in these studies are only available in a few countries/regions.[27,28] Our research found that 17% of DPN clinical trials and 18% of published DPN clinical trials were for pathogenetic treatments. However, there is currently no treatment that

Table 6 Overview of Interventions in 452 Clinical Trials on DPN

Interventional Categories	N=459	Percentage of Records (%)
Symptomatic Treatment of DPN		
Anticonvulsants	71	15.5
Antidepressants	40	8.7
Opioids	20	4.4
Pathogenetic Treatments		
Aldose reductase inhibitors	46	10.0
Vitamin and its derivatives	19	4.1
Antioxidative agent	18	3.9
Other Pharmacologic Agents		
Topical Medications	33	7.2
Vasodilator	13	2.8
Other pharmacologic agents	60	13.1
Device		
Management/Therapy system	1	0.2
Wearable aid	9	2.0
Laser treatment	3	0.7
Electrical stimulation	31	6.8
Monochromatic infrared energy (MIRE)	9	2.0
Exercise	40	8.7
Medical food	5	1.1
Massage/Acupuncture	24	5.2
Genetic/Biological therapy	17	3.7

can prevent or reverse DPN; instead, treatment is limited to pain management.[27,28] In addition, our results revealed that 34% of DPN clinical trials and 29% of published DPN clinical trials were for symptomatic treatment. In our study, drugs were the most commonly used intervention, followed by devices, and then drug studies focused on anticonvulsants, aldose reductase inhibitors, and antidepressants. However, drugs for neuropathic pain are associated with many side effects, such as nausea, dizziness, dry mouth, and weight gain, which occur in 40% of the population and are dose-dependent.[29] Due to changes in the pathogenesis of DPN, the efficacy of ARIs may be limited.[30] Although many ARIs have been successfully developed in in vivo and in vitro experiments, they have failed in most clinical trials due to adverse drug reactions and inadequate efficacy.[31]

The safety and effectiveness of medical products need to be reviewed before they are used in the general population, which is supervised and implemented by the Food and Drug Administration (FDA). Drugs can be approved by the FDA in a variety of ways.[32] FDA approval of a new drug is associated with an increase in the publication of clinical trial registrations and reports of results for the drug.[33] However, the failure of new DPN drugs approved by the FDA may be related to the low annual registration rate of clinical trials, the delay in reporting test results, the low publication rate of articles or the stage of the clinical trial. Therefore, in future research, we should develop drugs based on the pathogenesis of DPN and reduce side effects. External treatments of DPN include topical drug therapies and device treatments. For patients who cannot tolerate oral medications, topical medication is a good choice. The most common local analgesics are lidocaine, capsaicin, and amitriptyline.[29] Lidocaine patches can improve the quality of life of patients with DPN, and their efficacy is equivalent to that of pregabalin.[34] Capsaicin can reduce pain and improve sleep quality in patients with DPN.[35] Our study found that 11 clinical trials investigated topical drugs as interventions, and 7% of the published clinical trials involved topical drug therapies. Topical drug therapies are safe and effective and are a valuable choice for the treatment of DPN. Due to oral drug intolerance and the high proportion of elderly patients, the development of topical drugs has great potential.[10,36]

Research on device treatments has shown that high-frequency spinal cord stimulation is a safe and effective means of providing analgesia, and pulsed electromagnetic fields can regulate neuropathic pain and nerve impulses.[37] Plantar electrical stimulation can improve the ankle brachial index and enhance motor ability and plantar sensation in patients with DPN.[21] In this study, we found that electrical stimulation device studies accounted for half of the studies on devices. Electrical stimulation has no contraindications or side effects and may be an effective alternative and adjuvant therapy for DPN.[38]

Conclusions and Future Perspectives

This report is the first summary of the registration of DPN clinical trials in the ICTRP Registration Platform and the

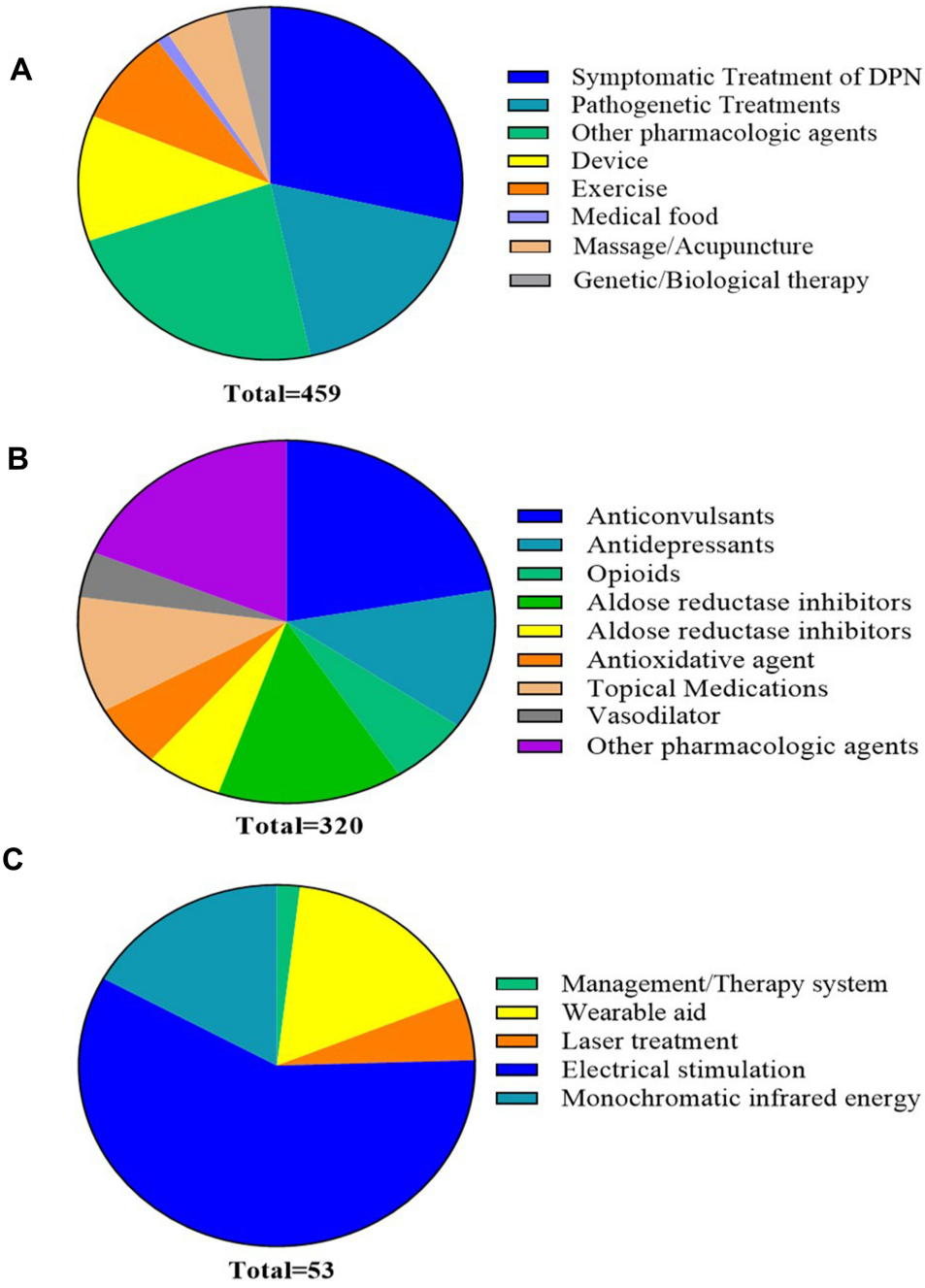

Figure 5 Intervention characteristics in 452 published clinical trials on DPN. (**A**) Intervention categories in 452 published clinical trials on DPN; (**B**) drug interventions in 315 published clinical trials on DPN; (**C**) device interventions in 52 published clinical trials on DPN.

current situation of DPN clinical studies. We found that the sample size of most DPN clinical trials was usually small and conducted in a single center. In addition, the clinical registration information and results were not updated in a timely manner. Most clinical trials have focused on drug interventions, and symptomatic treatment accounts for approximately 30% of interventional DPN clinical trials. However, given the lack of understanding of the pathogenesis of DPN, the treatment of the pathogenesis was the focus in only approximately 17.5% of clinical trials. The main evaluation indicators at this stage were pain or clinical symptoms.

However, this summary for DPN clinical trials had several limitations. First, we cannot guarantee the absolute reliability of the results. We only provide an overview of the characteristics of the clinical trials on DPN. We did not have access to the complete trial plans and data, and we were unable to evaluate the shortcomings and advantages

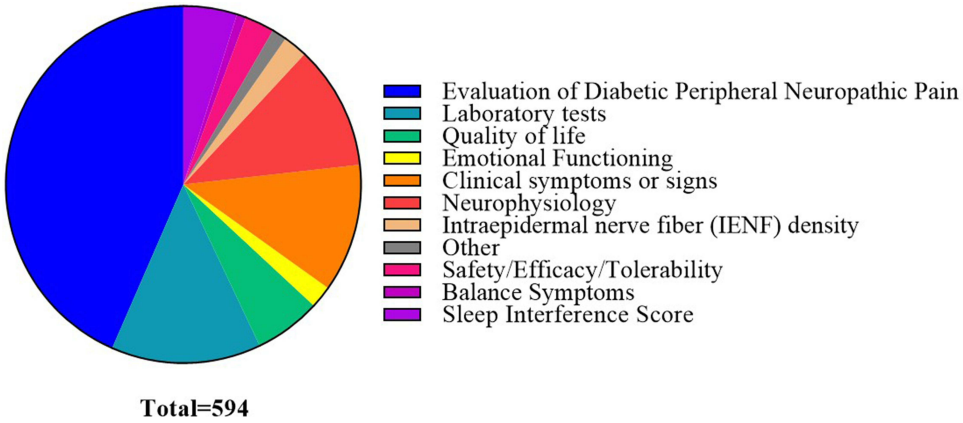

Figure 6 Outcomes in 586 published clinical trials on DPN.

of the trials. Second, we only retrieved publications from 22 trials. There may be more clinical trials to be published, but we did not contact the main investigators to verify the situation. Third, we only identified published clinical trials on DPN in the PubMed and Web of Science databases, and we may therefore have missed some published clinical trials.

In the future, we hope that more multicenter, large-sample, placebo-controlled, randomized DPN clinical trials would provide high-quality clinical evidence. In addition to pain scores, comprehensive outcome indicators such as quality of life, quality of sleep, and psychological status should be considered as secondary outcomes. Collectively, this study could provide a reference and new insights for future DPN interventional trials.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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