Intervencije za liječenje neuropatske boli : analiza najviše razine dokaza i načina procjene intervencija

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Mentorica: izv. prof. dr. sc. Livia Puljak, dr. med.

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1 SADRŽAJ

2 POPIS OZNAKA I KRATICA

AC1	Gwetov AC1 koeficijent podudarnosti među ocjenjivačima
AMSTAR	Ljestvica za procjenu metodološke kvalitete sustavnih pregleda (engl. *Assessment of Multiple Systematic Reviews*)
BDI	Beckov inventar depresije (engl. *Beck Depression Inventory*)
CDSR	Cochraneova baza sustavnih pregleda (engl. *Cochrane Database of Systematic Reviews*)
CI	Raspon pouzdanosti (engl. *confidence interval*)
CINAHL	Elektronička baza podataka CINAHL (engl. *Cumulative Index to Nursing and Allied Health Literature*)
DARE	Elektronička baza podataka DARE (engl. *Database of Abstracts of Reviews of Effects*)
HADS	Ljestvica bolničke anksioznosti i depresije (engl. *Hospital Anxiety Depression Scale*)
IASP	Međunarodno udruženje za istraživanje boli (engl. *International Association for the Study of Pain*)
IMMPACT	Inicijativa za metode, mjere i procjenu boli u kliničkim pokusima (engl. *the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials*)
IQR	Interkvartilini raspon (engl. *Interquartile range*)
MEDLINE	Bibliografska baza američke Nacionalne medicinske knjižnice (engl. *Medical Literature Analysis and Retrieval System Online*)
MeSH	Baza podataka predmetnica naziva *Medical subject heading*
NeuPSIG	Posebna radna skupina o neuropatskoj boli IASP-a (engl. *Special Interest Group on Neuropathic Pain*)
NRS	Numerička ljestvica procjene boli (engl. *Numerical Rating Scale)*

PGIC	Ispitanikova globalna procjena promjene (engl. *Patient Global Impression of Change*)
POMS	Profil stanja raspoloženja (engl. *Profile of Mood States*)
PRISMA	PRISMA smjernice za prikazivanje sustavnih pregleda i meta-analiza (engl. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*)
PROSPERO	Međunarodni prospektivni registar za sustavne preglede (engl. *International Prospective Register of Systematic Reviews*)
PsycINFO	Elektronička baza podataka PsycINFO (engl. *Psychological Information Database*)
R-AMSTAR	Revidirana ljestvica AMSTAR za procjenu metodološke kvalitete sustavnih pregleda (engl. *Revised AMSTAR*)
ROBIS	Alat za procjenu rizika pristranosti u sustavnim pregledima (engl. *Risk of Bias in Systematic Reviews*)
rTMS	Repetitivna transkranijalna magnetna stimulacija
SF-36	Upitnik kvalitete života *Medical Outcomes Survey Short Form*
TCA	Triciklički antidepresivi
VAS	Vizualno-analogna ljestvica za mjerenje boli (engl. *Visual Analogue Scale*)
VRS	Verbalna ljestvica za mjerenje boli (engl. *Verbal Rating Scale*)

3 PREGLED OBJEDINJENIH RADOVA

Ova doktorska disertacija temelji se na objedinjenim znanstvenim radovima:

1. Dosenovic S, Jelicic Kadic A, Miljanovic M, Biocic M, Boric K, Cavar M, i sur. Interventions for Neuropathic Pain: An Overview of Systematic Reviews. Anesth Analg. 2017;125(2):643-52. Epub 2017/07/22. doi: 10.1213/ANE.0000000000001998.

2. Dosenovic S, Jelicic Kadic A, Jeric M, Boric M, Markovic D, Vucic K, i sur. Efficacy and Safety Outcome Domains and Outcome Measures in Systematic Reviews of Neuropathic Pain Conditions. Clin J Pain. 2018;34(7):674-84. Epub 2017/12/19. doi: 10.1097/AJP.0000000000000574.

3. Dosenovic S, Jelicic Kadic A, Vucic K, Markovina N, Pieper D, Puljak L. Comparison of methodological quality rating of systematic reviews on neuropathic pain using AMSTAR and R-AMSTAR. BMC Med Res Methodol. 2018;18(1):37. Epub 2018/05/10. doi: 10.1186/s12874-018-0493-y.

3.1 UVOD

Neuropatska bol nastaje kao posljedica oštećenja ili bolesti somatosenzornog živčanog sustava (1) i pogađa između 5 i 10% opće populacije (2-4). Epidemiološka istraživanja su pokazala da mnogi oboljeli od neuropatske boli nisu prikladno liječeni (5). Međunarodno udruženje za istraživanje boli (engl. *International Association for the Study of Pain*, IASP) stoga smatra ublažavanje neuropatske boli prioritetnim zdravstvenim problemom (6).

Tijekom posljednjih godina izdano je nekoliko kliničkih smjernica utemeljenih na dokazima iz randomiziranih kontroliranih istraživanja o farmakološkom liječenju neuropatske boli (5, 7-9). Te smjernice su ukazale na manjkavosti u postojećoj bazi znanja dobivenog na temelju kliničkih istraživanja, a ponekad su došle do različitih zaključaka zbog metodoloških razlika u procjeni postojećih dokaza (10). Nadalje, često se kao dodatna mogućnost ili kao dodatak farmakološkim intervencijama koriste druge intervencije (kirurške i ostale, tzv. nefarmakološke) budući da neki ispitanici ne postižu zadovoljavajući klinički odgovor ili razviju nepodnošljive nuspojave na farmakološko liječenje (11, 12). Posljednje kliničke smjernice o intervencijskom liječenju neuropatske boli izdala je 2013. godine Posebna radna skupina o neuropatskoj boli IASP-a (engl. *Special Interest Group on Neuropathic Pain,* NeuPSIG); u tim se smjernicama navodi da se mnoge intervencije za liječenje refraktorne neuropatske boli temelje na dokazima slabe kvalitete (12).

Sustavni pregledni radovi imaju ključnu ulogu u medicini utemeljenoj na dokazima jer odgovaraju na specifično pitanje na sustavan, transparentan i ponovljiv način. Osobine kvalitetnog sustavnog pregleda su unaprijed registriran protokol, sveobuhvatno pretraživanje višestrukih izvora podataka, procjena kvalitete uključenih studija te pomna interpretacija rezultata. Oni pružaju odgovore bolesnicima i kliničarima, tvore temelj smjernica utemeljenih na dokazima i pomažu oblikovati zdravstvenu politiku (13).

Iako postoji sve veći broj sustavnih pregleda randomiziranih kontroliranih istraživanja o različitim intervencijama za liječenje neuropatske boli, njihove rezultate ponekada je teško protumačiti, zaključci im mogu biti nepodudarni i ograničeni kvalitetom uključenih istraživanja, kao i kvalitetom samog sustavnog pregleda (10). Zbog toga je od iznimne važnosti kritička procjena metodološke kvalitete postojećih sustavnih preglednih članaka, najčešće pomoću ljestvica AMSTAR (engl. *Assessment of Multiple Systematic Reviews*) (14) i R-AMSTAR (engl. *Revised AMSTAR*) (15).

Nadalje, korištenje različitih domena i mjera ishoda u randomiziranim kontroliranim istraživanjima i sustavnim preglednim radovima također otežava usporedbu učinkovitosti i sigurnosti istraživanih intervencija za liječenje neuropatske boli. Standardizacija domena ishoda i mjera ishoda u randomiziranim kontroliranim pokusima i sustavnim pregledima omogućila bi jednostavniji ustroj i recenziranje istraživačkih protokola, pojednostavila i osnažila izradu sustavnih pregleda te pomogla kliničarima u donošenju odluka. Inicijativa za metode, mjere i procjenu boli u kliničkim pokusima (engl. *the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials*, IMMPACT) preporučila je 2003. godine šest ključnih domena ishoda koje bi se trebale analizirati u kliničkim pokusima o kroničnoj boli u odraslih, ali i u sustavnim pregledima kliničkih pokusa o kroničnoj boli u odraslih (16). Tih šest ključnih domena ishoda su: i) bol, ii) tjelesno funkcioniranje, iii) emocionalno funkcioniranje, iv) ispitanikova ocjena poboljšanja i zadovoljstvo liječenjem, v) simptomi i nuspojave, vi) dispozicija ispitanika (pridržavanje liječenju i razlozi za prijevremeno povlačenje iz istraživanja) (16). Konsenzus je također postignut za dodatne domene ishoda (kliničarova ili zamjenska ocjena poboljšanja, funkcioniranje u ulozi, farmakoekonomske mjere i biološki markeri), a naglašeno je da se preporučene domene ishoda mogu nadopuniti dodatnim ishodima koji se smatraju važnima za pojedinu vrstu liječenja (16). Iako autori nisu ograničeni korištenjem preporučenog ključnog skupa ishoda definiranog za istraživano stanje, pridržavanje i prijavljivanje ključnog skupa ishoda trebalo bi biti prioritetno (17).

Dvije godine nakon objavljivanja ključnih domena ishoda, IMMPACT inicijativa je preporučila ključne mjera ishoda za procjenu ključnih domena ishoda (18). Objavljivanje nekorisnih istraživanja (engl. *research waste*) i dalje će se nastaviti ukoliko se ne koristi odgovarajući preporučeni ključni skup ishoda za procjenu učinkovitosti ispitivanih intervencija u kliničkim istraživanjima i sustavnim pregledima iz tog područja (19).

Nakon razvijanja ključnog skupa ishoda važno je periodično provjeriti njegovo korištenje kako bi se ustanovilo jesu li predložene domene i mjere ishoda i dalje važne, treba li ih nadopuniti novim domenama i mjerama ishoda, je li postupak uvođenja bio uspješan i je li potrebno uključiti nove sudionike u razvoj ključnog skupa ishoda (20).

Otvorena pitanja i nedostatke u postojećim dokazima moguće je istražiti provođenjem sustavnog pregleda sustavnih preglednih radova (engl. *overview of systematic reviews*). Prednost te vrste istraživanja je sažimanje postojećih dokaza iz sustavnih pregleda o određenom istraživačkom pitanju, čime se može smanjiti nesigurnost pri donošenju odluka i

stvoriti nova hijerarhija u piramidi dokaza (21). Također, takva istraživanja mogu ukazati na potrebu za provođenjem novih kontroliranih istraživanja i sustavnih pregleda i na nedostatak uvjerljivih zaključaka provedenih sustavnih preglednih radova (22).

Budući da liječenje neuropatske boli predstavlja klinički izazov te postoje nepodudarnosti u preporukama iz različitih sustavnih pregleda, važno je sažimanje i kritička procjena kvalitete postojećih dokaza temeljenih na sustavnim preglednim radovima, što do sada nije napravljeno.

Korištenje ključnog skupa ishoda potrebno je i u kliničkim pokusima i u sustavnim pregledima iz određenog područja. Niti jedno istraživanje do sada nije procijenilo korištenje cijelog ključnog skupa ishoda te ključnih mjera ishoda IMMPACT inicijative za kroničnu bol u sustavnim pregledima o neuropatskoj boli. Nadalje, nisu istraženi znanje i stavovi autora sustavnih pregleda glede preporučenih domena i mjera ishoda.

Ova doktorska disertacija temelji se na četiri provedena istraživanja koja čine povezanu cjelinu. U prvom istraživanju napravljen je sustavni pregled kako bi se pronašli svi sustavni pregledi o intervencijama za ublažavanje neuropatske boli. U drugom dijelu istraživano je korištenje domena ishoda i mjera ishoda u sustavnim pregledima za procjenu učinkovitosti i sigurnosti intervencija za neuropatsku bol, a rezultati su uspoređeni s ishodima koje preporučuje IMMPACT inicijativa za kroničnu bol. Treći dio usmjeren je na metodološku kvalitetu sustavnih pregleda o intervencijama za ublažavanje neuropatske boli te uspoređuje dvije mjerne ljestvice za procjenu kvalitete. Kao četvrti dio disertacije provedeno je primarno istraživanje procjene primjerenosti ključnih ishoda u sustavnim pregledima o intervencijama za neuropatsku bol među autorima sustavnih pregleda.

3.2 CILJEVI OBJEDINJENIH RADOVA

Ciljevi objedinjenih istraživanja su:

i) sažeti dokaze iz sustavnih pregleda randomiziranih kontroliranih istraživanja o učinkovitosti i sigurnosti intervencija za ublažavanje neuropatske boli;

ii) analizirati metodološku kvalitetu te usporediti dvije ljestvice za procjenu metodološke kvalitete sustavnih pregleda o neuropatskoj boli (AMSTAR i R-AMSTAR);

iii) analizirati domene i mjere ishoda korištene za procjenu učinkovitosti i sigurnosti intervencija te procijeniti korištenje ključnog skupa ishoda IMMPACT inicijative za kroničnu bol u sustavnim pregledima o neuropatskoj boli; i

iv) istražiti znanja i stavove autora sustavnih pregleda o ključnom skupu ishoda i ključnim mjerama ishoda za kroničnu bol koje preporučuje IMMPACT inicijativa.

3.3 PREGLED METODOLOGIJE OBJEDINJENIH RADOVA

3.3.1 Rad 1. Intervencije za liječenje neuropatske boli: sustavni pregled sustavnih preglednih radova

U prvom dijelu istraživanja proveden je sustavni pregled sustavnih preglednih radova za koji je objavljen protokol broj CRD42015025831 u bazi PROSPERO (engl. *International Prospective Register of Systematic Reviews*). Istraživanje je napravljeno prema PRISMA smjernicama (engl. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) (23).

Definirana je sveobuhvatna strategija pretraživanja za elektroničku bazu podataka MEDLINE (engl. *Medical Literature Analysis and Retrieval System Online*, Dodatak 1) kako bi se pronašli svi sustavni pregledi (s ili bez meta-analize) randomiziranih kontroliranih pokusa o neuropatskoj boli prema IASP-ovoj definiciji (24). Uključene su sve vrste intervencija, komparatora i mjera ishoda. Pretraživanje je napravljeno kombiniranjem MeSH predmetnica (engl. *medical subject heading*) i slobodno odabranih ključnih riječi za neuropatsku bol i sustavni pregled/meta-analizu. Ta je strategija pretraživanja zatim prilagođena za sljedeće baze podataka: Cochraneovu bazu sustavnih pregleda (engl. *Cochrane Database of Systematic Reviews*, CDSR), DARE (engl. *Database of Abstracts of Reviews of Effects*), CINAHL (engl. *Cumulative Index to Nursing and Allied Health Literature*) i PsycINFO (engl. *Psychological Information Database*). Pretražena su sva izdanja od osnutka do ožujka 2015., bez postavljanja jezičnog ograničenja.

Dva istraživača su zasebno pregledala sve dobivene naslove, sažetke i cjelovite tekstove radova relevantnih za temu istraživanja. Razlike su razriješene diskusijom i uključenjem trećeg istraživača. Iz uključenih radova dvoje istraživača je neovisno izvuklo unaprijed definirane podatke te ih unijelo u Microsoft Excel program (Microsoft Inc., Redmond, WA, SAD). Razlike u ekstrakciji podataka razriješio je treći istraživač. Prikupljeni su sljedeći podatci: autori, datum objavljivanja, zemlja iz koje potječe sustavni pregled, pretraživane baze podataka, istraživane intervencije i komparatori, postojanje meta-analize, izvor financiranja, osobine ispitanika, opis neuropatske boli, način dijagnosticiranja neuropatske boli, trajanje liječenja i trajanje praćenja ispitanika, rezultati i zaključci iz sažetaka.

Učinjena je detaljna deskriptivna analiza dobivenih podataka. Zaključke iz sažetaka o učinkovitosti i sigurnosti kategoriziralo je dvoje istraživača neovisno, a razlike su riješene diskusijom s trećim istraživačem. Za kategorizaciju su korištene modificirane kategorije

zaključaka temeljene na radu Tricco i sur. (25): i) pozitivno, ii) pozitivno-nedorečeno, iii) nedostaju dokazi, iv) bez mišljenja, v) jednako (kad je uspoređivano više intervencija), vi) jednako-nedorečeno (kad je uspoređivano više intervencija), vii) negativno, viii) negativno-nedorečeno, i ix) nejasno, potrebno je daljnje istraživanje.

Nedorečene su bile kategorije za koje su autori izjavili da je potrebno daljnje istraživanje za potvrdu njihovih rezultata ili da su nađeni dokazi niske kvalitete temeljem procjene kvalitete dokaza validiranim ljestvicama.

3.3.2 Rad 2. Domene ishoda i mjere ishoda korištene za procjenu učinkovitosti i sigurnosti istraživanih intervencija za neuropatsku bol u sustavnim pregledima

U drugom dijelu provedeno je presječno istraživanje korištenja domena ishoda i mjera ishoda za procjenu učinkovitosti i sigurnosti ispitivanih intervencija za liječenje neuropatske boli u sustavnim pregledima pronađenima u prvom istraživanju. Protokol ovog istraživanja objavljen je u bazi PROSPERO (CRD42015025833).

Korištene domene ishoda i mjere ishoda dvoje je istraživača neovisno prikupilo, a treći istraživač je razriješio razlike. Treći istraživač je također kategorizirao ishode u domene prema IMMPACT preporukama (16). Napravljena je usporedba korištenih domena ishoda prije i nakon 2005. god. kako bi se procijenio vremenski trend u korištenju preporučenih ishoda za procjenu učinkovitosti i sigurnosti.

Rezultati su uspoređeni s preporučenim ključnim skupom ishoda (objavljenim 2003. godine) i ključnim mjerama ishoda (objavljenima 2005.godine) koje je definirala IMMPACT inicijativa te prikazani deskriptivno pomoću programa Microsoft Excel (Microsoft Corp, Redmond, WA, SAD).

3.3.3 Rad 3. Procjena metodološke kvalitete sustavnih pregleda o intervencijama za ublažavanje neuropatske boli te usporedba mjernih ljestvica AMSTAR i R-AMSTAR

Za treći dio istraživanja objavljen je protokol u bazi PROSPERO (CRD42015025832). U ovom je istraživanju procijenjena metodološka kvaliteta sustavnih pregleda o neuropatskoj boli uključenih u prvo istraživanje. Kvaliteta sustavnih pregleda rađenih prema metodologiji Cochranea uspoređena je s ostalim sustavnim pregledima. Također su uspoređene dvije mjerne ljestvice za procjenu metodološke kvalitete sustavnih pregleda temeljenih na randomiziranim kontroliranim istraživanjima: AMSTAR i R-AMSTAR.

Prije procjene kvalitete čestice obaju ljestvica su objašnjenje istraživačima (jedan kliničar i jedan metodolog) bez prethodnog iskustva u njihovu korištenju, a nakon toga napravljena je probna procjena na jednom sustavnom pregledu koji je isključen iz analize. Dvoje istraživača je nakon kalibracijske vježbe izvršilo neovisnu procjenu kvalitete, a treći istraživač je razriješio razlike. Prvo je izvršena procjena svih sustavnih pregleda pomoću ljestvice AMSTAR (raspon bodova 0-11, svaka čestica boduje se s 0 ili 1 bod), a zatim pomoću ljestvice R-AMSTAR (raspon bodova 11-44, svaka čestica boduje se s 1-4 boda).

Sveukupna procjena svake od 11 AMSTAR čestica napravljena je gledajući udio sustavnih pregleda ocjenjenih s „da“ (1 bod) u ukupnom broju studija. Sveukupna procjena svake od 11 R-AMSTAR čestica napravljena je računajući udio sustavnih pregleda s najvišom ocjenom 4 u ukupnom broju sustavnih pregleda.

Ocjene dobivene na obje ljestvice pretvorene su u percentile kako bi se omogućila usporedba rezultata dobivenih različitim ljestvicama. Prvo su rangirani rezultati pojedine ljestvice od najnižeg prema najvišem, a zatim su dodijeljene zamjenske ocjene A-D: ocjena A ≥90. percentil, ocjena B 80-89. percentil, ocjena C 70-79. percentil, ocjena D ≤69. percentil, kao što je opisano ranije (15). Podudarnost među ocjenjivačima ocijenjena je pomoću Gwetovog AC1 koeficijenta (26), a koeficijenti podudarnosti su kategorizirani prema Landisu i Kochu (27).

Rezultati su prikazani kao apsolutne i relativne frekvencije, a ukupni zbrojevi pomoću medijana i interkvartilnog raspona.

3.3.4 Rad 4. Istraživanje primjerenosti ključnih domena ishoda i mjera ishoda IMMPACT inicijative među autorima sustavnih pregleda o intervencijama za ublažavanje neuropatske boli

U četvrtom dijelu disertacije provedeno je presječno istraživanje kojim je procijenjena primjerenost ključnih domena ishoda i mjera ishoda koje je preporučila IMMPACT inicijativa među autorima sustavnih pregleda o intervencijama za ublažavanje neuropatske boli.

Istraživanje je odobrilo Etičko povjerenstvo Medicinskog fakulteta Sveučilišta u Splitu (Ur. Br. 2181-198-03-04-18-007). Napravljen je 24-djelni upitnik na engleskom jeziku (Dodatak 2) i postavljen na mrežnu stranicu za anketiranje Survey Monkey (SurveyMonkey Inc, Palo Alto, CA, SAD). Upitnik je započeo informiranim pristankom ispitanika bez kojega nije bilo moguće pristupanje pitanjima. Nakon ispunjavanja općih pitanja o osobinama ispitanika

postavljena su specifična pitanja o ključnom skupu ishoda i ključnim mjerama ishoda IMMPACT inicijative. Ispitanici su zatim ocijenili važnost ponuđenih domena ishoda i mjera ishoda koje preporučuje IMMPACT inicijativa na ordinalnoj ljestvici 1-9 (1 = nevažno, 9 = od kritične važnosti). Smatralo se da je konsenzus o uključenju ishoda u ključni skup ishoda postignut za ishode koje 70% ili više ispitanika ocijeni 7-9 (ključna važnost) i manje od 15% ocijeni 1-3 (ograničena važnost) (20).

Prikupljene su adrese elektroničke pošte svih autora sustavnih pregleda koji su uključeni u prvo istraživanje te im je odaslana poveznica za ispunjavanje upitnika. Anonimnost sudionika osigurana je slanjem poveznice na upitnik putem elektroničke pošte. Adrese elektroničke pošte dopisnog autora nađene su u objavljenim radovima, a adrese ostalih autora nađene su putem Interneta. Dvoje istraživača je prikupilo elektroničke adrese, a treći istraživač je provjerio točnost prikupljenih podataka te odaslao upitnike. Program Microsoft Excel (Microsoft Corp, Redmond, WA, SAD) korišten je za deskriptivne analize. Podatci su prikazivani kao apsolutne i relativne frekvencije.

3.4 PREGLED REZULTATA OBJEDINJENIH RADOVA

3.4.1 Rad 1. Intervencije za liječenje neuropatske boli: sustavni pregled sustavnih preglednih radova

Rezultati pretraživanja literature

Pretraživanjem literature nađeno je 2412 naslova i sažetaka, od kojih je 2070 isključeno nakon probira, a 342 cjelovita teksta ostavljena su za daljnji probir. Konačno je uključeno 97 sustavnih pregleda, od kojih je 7 bilo bez uključenih randomiziranih kontroliranih istraživanja (engl. *empty review*).

Karakteristike sustavnih pregleda

Sustavni pregledi su objavljeni između 1995. i 2015. god i uključili su od 0 do 174 randomizirana kontrolirana istraživanja. Detalje o vrsti neuropatske boli navela su 53 uključena sustavna pregleda, a najčešće su istraživane intervencije za bolnu dijabetičku polineuropatiju (25%), lumbosakralnu radikulopatiju (16%) i sve vrste neuropatske boli (11%). Samo je 36 sustavnih pregleda navelo kriterije za dijagnosticiranje neuropatskog bolnog stanja. Najčešće su istraživane farmakološke (59%) i kirurške (15%) intervencije za liječenje neuropatske boli.

Najkraće praćenje trajalo je 45 minuta u sustavnom pregledu o infuziji ketamina za fantomsku bol, a najdulje 74 mjeseca u sustavnom pregledu o radiofrekventnoj termokoagulaciji Gasserovog ganglija za liječenje klasične trigeminalne neuralgije. Dvadesetšest od 90 (29%) sustavnih pregleda koji su sadržavali uključene randomizirane pokuse nije navelo trajanje liječenja, a 22 (24%) sustavna pregleda nisu navela trajanje praćenja ispitanika.

Metodološka kvaliteta

Trećina sustavnih pregleda (34%) bila je visoke metodološke kvalitete (AMSTAR zbroj ≥ 8/11), preko polovine (57%) bili su srednje kvalitete (AMSTAR zbroj 4-7/11) i 9% niske kvalitete (AMSTAR zbroj 0-3/11).

Uvjerljivost dokaza

Više od pola zaključaka (54%) o učinkovitosti i oko 80% zaključaka o sigurnosti ispitivanih intervencija nađenih u sažetcima bilo je nedorečeno. Učinkovite intervencije nađene su za liječenje bolne dijabetičke polineuropatije [pregabalin, gabapentin, određeni triciklički antidepresivi (TCAi), opioidi, antidepresivi i antikonvulzivi], postherpetičke neuralgije

(gabapentin, pregabalin, određeni TCAi, antidepresivi i antikonvulzivi, opioidi, natrij valproat, topikalni kapsaicin i lidokain), lumbalne radikularne boli (epiduralni kortikosteroidi, repetitivna transkranijalna magnetna stimulacija (rTMS), discektomija), cervikalne radikularne boli (rTMS), sindroma karpalnog kanala (kirurška dekompresija), sindroma kubitalnog kanala (kirurška dekompresija i transpozicija ulnarnog živca), trigeminalne neuralgije (karbamazepin, lamotrigin i pimozid za refraktorne slučajeve, rTMS), neuropatije povezane s HIVom (topikalni kapsaicin) i središnje neuropatske boli (određeni TCAi, lamotrigin i pimozid za refraktorne slučajeve, rTMS). Preporuke najčešće nisu mogle biti donesene zbog nedostatka dokaza ili zbog niske kvalitete dostupnih dokaza.

Dokazi visoke kvalitete

Postoje dokazi iz sustavnih pregleda visoke kvalitete da su opioidi bolji od placeba; i da su gabapentin i TCAi jednako učinkoviti u liječenju bolne dijabetičke neuropatije i postherpetičke neuralgije. Topikalni 8% kapsaicin je učinkovit u postherpetičkoj neuralgiji i perifernoj neuropatiji povezanoj s HIV-om. Inhibitori aldoza-reduktaze nisu učinkoviti u liječenju bolne dijabetičke neuropatije. Nije pronađeno uvjerljivih dokaza o učinkovitosti nortriptilina u nekoliko bolnih neuropatskih stanja. Različite kirurške tehnike za liječenje kompresivnih neuropatija (sindrom karpalnog i kubitalnog kanala) pružile su podjednako smanjenje simptoma.

Dokazi srednje kvalitete

Pregabalin, topiramat i okskarbazepin su učinkovitiji od placeba u liječenju bolne dijabetičke neuropatije. Dobru učinkovitost u postherpetičkoj neuralgiji pokazali su pregabalin, topikalni kapsaicin, opioidi, gabapentin, TCAi, lidokainski naljepak i valproat. Najveću dobrobit u liječenju kronične periferne neuropatske boli pružili su pregabalin i duloksetin. Karbamazepin se pokazao lijekom izbora za trigeminalnu neuralgiju. Topikalni 8% kapsaicin pokazao je učinkovitost u liječenju boli kod bolesnika s perifernom neuropatijom povezanoj s HIV-om, ali kanabis nije preporučen kao rutinski način liječenja. Epiduralno primijenjeni kortikosteroidi učinkoviti su u liječenju lumbalne radikularne boli, minimalno invazivna i otvorena discektomija rezultirale su podjednakim smanjenje boli i sličnom stopom komplikacija, a sustavno primijenjeni steroidi nisu se pokazali učinkovitima pa je preporučeno da se ne koriste u liječenju lumbalne radikularne boli. Usporedba endoskopskog i otvorenog otpuštanja pritiska medijanog živca u liječenju sindroma karpalnog kanala dovela je do različitih zaključaka za istraživane ishode. Jednostavna dekompresija ulnarnog živca

kao metoda kirurškog liječenja kompresije ulnarnog živca jednako je učinkovita kao i prednja transpozicija živca. Nađeni su pozitivni učinci TCAi, pregabalina i kanabinoida u liječenju centralne neuropatske boli.

Dokazi niske kvalitete

Temeljem dokaza niske kvalitete gabapentin je učinkovitiji od placeba u bolnoj dijabetičkoj neuropatiji, a antidepresivi i antiepileptici su jednako učinkoviti u smanjenju neuropatske boli kod dijabetičke neuropatije i postherpetičke neuralgije, iako je manja vjerojatnost da će ispitanici prestati liječenje antiepilepticima zbog nuspojava. Topikalni kapsaicin (niske i visoke koncentracije) pokazao je učinkovitost u liječenju periferne neuropatske boli. Repetitivna transkranijalna magnetna stimulacija pokazala se učinkovitom u liječenju lumbalne i cervikalne radikularne boli, trigeminalne neuralgije, neuropatske boli perifernog živca i centralne neuropatske boli.

Područja bez dokaza

Sedam sustavnih pregleda nije našlo niti jedno uključivo randomizirano kontrolirano istraživanje, stoga su to područja koja zahtijevaju pozornost istraživača: i) dekompresivni kirurški zahvati donjih udova za simetričnu bolnu dijabetičku neuropatiju, ii) farmakološko liječenje kronične idiopatske aksonalne polineuropatije, iii) imunosupresivno liječenje nesistemske vaskulitične neuropatije, iv) imunoterapija za idiopatsku lumbosakralnu pleksopatiju, v) transkutana električna stimulacija živca za fantomsku bol nakon amputacije, vi) imunoterapija za dijabetičku amiotrofiju i vii) liječenje idiopatske i nasljedne neuralgične amiotrofije (brahijalnog neuritisa).

3.4.2 Rad 2. Domene ishoda i mjere ishoda korištene za procjenu učinkovitosti i sigurnosti istraživanih intervencija za neuropatsku bol u sustavnim pregledima

Karakteristike sustavnih pregleda

U sustavnim pregledima korišteno je između 1 i 37 različitih mjera ishoda [(medijan (IQR): 9,5 (6-17,3)]. Ukupno je korišteno 240 različitih mjera ishoda za procjenu učinkovitosti i sigurnosti istraživanih intervencija za neuropatsku bol u 90 sustavnih pregleda koji su imali uključena randomizirana kontrolirana istraživanja. Nijedna mjera ishoda nije bila korištena u svim sustavnim pregledima.

Primarni ishod nije bio naveden u 28 (29%), a sekundarni u 43 (44%) od 97 sustavnih pregleda o neuropatskoj boli. Nijedan sustavni pregled nije naveo jesu li razmatrali ključni skup domena ishoda koji preporučuje IMMPACT za odabir važnih domena ishoda, tek ih se 9 osvrnulo na preporuke IMMPACT-a pri odabiru nekih korištenih mjera ishoda.

Domene ishoda u metodama

Medijan svih domena ishoda navedenih u metodama bio je 4 (IQR 3-5, raspon 0-9), a medijan planiranih ključnih domena ishoda bio je 3 (IQR 2-4, raspon 0-6). Samo 3 (3%) sustavna pregleda su planirala koristiti svih 6 IMMPACT-preporučenih ključnih domena ishoda. Najčešće je planirano korištenje dvaju ključnih domena ishoda: bol (n=77, 86%) i simptomi i nuspojave (n=68, 76%).

Tjelesno funkcioniranje planirano je kao domena ishoda u sustavnim pregledima objavljenima nakon siječnja 2005. dvaput češće (n=37, 46%) nego u sustavnim pregledima objavljenima prije tog datuma (n=2, 22%), a ispitanikova ocjena poboljšanja i zadovoljstva liječenjem 4 puta češće (n=40, 49% naspram n=1, 11%) u sustavnih pregledima objavljenima nakon siječnja 2005.

Domene ishoda u rezultatima

Medijan korištenih ključnih domena ishoda bio je 4 od mogućih 6 (IQR 2,8-5, raspon 1-6), a najčešće su prikazane domene bol (n=85, 94%) i simptomi i nuspojave (n=76, 84%). Samo je 10% (n=9) sustavnih pregleda prikazalo svih 6 ključnih domena ishoda, a četvrtina tek 1 ili 2 ključne domene ishoda. Medijan svih domena ishoda prikazanih u rezultatima bio je 5 (IQR 3-6, raspon 1-9).

Usporedba sustavnih pregleda objavljenih prije i nakon siječnja 2005. god. pokazala je da nijedan od 9 sustavnih pregleda objavljenih prije tog datuma nije prikazao rezultate za

ključnu domenu ishoda ispitanikova ocjena poboljšanja i zadovoljstva liječenjem, a 44 od 81 (54%) sustavnog pregleda objavljenog kasnije je koristilo tu domenu za procjenu učinkovitosti ispitivanih intervencija. Nije bilo vremenskih razlika u korištenju ostalih ključnih domena.

Mjere ishoda korištene za ocjenu IMMPACT ključnih domena ishoda

Za procjenu domene *boli* korištena je 61 mjera ishoda. Jačina boli najčešće je mjerena pomoću Vizualno-analogne ljestvice (engl. *Visual Analogue Scale*, VAS, n=59) i Numeričke ljestvice procjene boli (engl. *Numerical Rating Scale*, NRS, n=29). Smanjenje boli izraženo je najčešće kao 50-postotno smanjenje početne razine boli u 58 (64 %) te kao 30-postotno smanjenje na VAS-u, NRS-u ili nedefiniranoj ljestvici za bol u 32 (36%) sustavna pregleda.

Tjelesno funkcioniranje procijenjeno je pomoću 74 mjere ishoda, a najčešće su korištene Kratki upitnik kvalitete života SF-36 (engl. *Medical Outcomes Survey Short Form*, n=18), Oswestry indeks invalidnosti (engl. *Oswestry Disability Index*, n=14), Roland-Morris upitnik invalidnosti (engl. *Roland-Morris disability questionnaire*, n=11), snaga hvata šake (n=14) i promjene u zbroju bodova kvalitete sna (n=9).

Trinaest mjera ishoda upotrijebljeno je za procjenu ključne domene *emocionalnog funkcioniranja*. Beckov inventar depresije (engl. *Beck Depression Inventory*, BDI), Profil promjena raspoloženja (engl. *Profile of Mood States*, POMS), Ljestvica bolničke anksioznosti i depresije (engl. *Hospital Anxiety Depression Scale*, HADS) i Ljestvica procjene ishoda karpalnog tunela, duševna bol (engl. *Carpal Tunnel Outcome Assessment, Mental Distress*) su najčešće prikazane mjerne ljestvice (korištene svaka u n = 3 sustavna pregleda).

Ključna domena ishoda *ispitanikova ocjena poboljšanja i zadovoljstva liječenjem* iskazana je kao "mnogo ili vrlo mnogo poboljšano" na ljestvici *Patient Global Impression of Change* (PGIC) u 11 sustavnih pregleda, a nakon toga kao „klinički značajno poboljšanje" na ljestvici PGIC u 7 sustavnih pregleda. Ostale mjere ishoda (npr. *Global Perceived Effect*) su rjeđe korištene.

Simptomi i nuspojave, peta ključna domena ishoda, prijavljivani su najviše kao učestalost (n=70) i ozbiljnost (n=60) nuspojava ispitivanih intervencija za liječenje neuropatske boli, a čak 13 uključenih studija samo je navelo nuspojave bez detaljnijeg pojašnjenja njihove učestalosti ili ozbiljnosti.

Polovina (n=45) sustavnih pregleda istražilo je šestu ključnu domenu *dispozicija ispitanika*, 38 (42%) kao preuranjeno povlačenje ispitanika iz istraživanja zbog nuspojava, a 18 (20%) kao preuranjeno povlačenje ispitanika zbog nedostatka učinkovitosti istraživanog liječenja.

Dodatne domene ishoda

Domena kliničarova ili zamjenska ocjena globalnog poboljšanja (npr. broj ispitanika dobrog ili odličnog poboljšanja, kliničarov dojam oporavka) korištena je za procjenu učinkovitosti istraživanih intervencija u trećini sustavnih pregleda o neuropatskoj boli. Funkcioniranje u ulozi (npr. posao, edukacija) prikazano je u 19/90 (21%) sustavnih pregleda, najčešće kao status na poslu, a samo je jedan (1,1%) sustavni pregled istraživao funkcioniranje u društvu. Domenu farmakoekonomske mjere koristilo je samo šest (6,7%) sustavnih pregleda, ali su zato biološki markeri često istraživani (n=38, 42%).

Ostali ishodi

Ishodi koji se nisu mogli kategorizirati u ključne ili dodatne domene IMMPACT-a su učestalost reoperacije (n=11, 12%), potreba za kirurškim zahvatom kao mjera učinkovitosti konzervativnog liječenja (n=9, 10%), trajanje zahvata (n=7, 7,8%), stopa povrata (n=5, 5,6%) i duljina bolničkog boravka (n=4, 4,4%).

3.4.3 Rad 3. Procjena metodološke kvalitete sustavnih pregleda o intervencijama za ublažavanje neuropatske boli te usporedba mjernih ljestvica AMSTAR i R-AMSTAR

Metodološka kvaliteta i ispunjavanje pojedinih čestica AMSTAR i R-AMSTAR ljestvice

Rezultati trećeg istraživanja pokazali su da metodološka kvaliteta analiziranih sustavnih pregleda o neuropatskoj boli nije optimalna, neovisno je li za procjenu korištena ljestvica AMSTAR ili R-AMSTAR [medijan 6/11 (IQR: 5-8) na AMSTAR-u i 30/44 (IQR: 26-35) na R-AMSTAR-u]. Slične rezultate dala je procjena kvalitete temeljena na zamjenskim ocjenama A-D. Najnižu ocjenu D dobila je većina sustavnih pregleda (64 prema AMSTAR ljestvici, 68 prema R-AMSTAR ljestvici).

Sustavni pregledi su dobili najbolje ocjene za AMSTAR česticu 3 (sveobuhvatno pretraživanje literature, 98% ispunjeno), 7 (znanstvena kvaliteta procijenjena i dokumentirana, 89% ispunjeno) i 9 (korištene primjerene metode objedinjenja rezultata, 80% ispunjeno). Nasuprot tome, najgore ocjenjene čestice su bile 11 (uključen sukob interesa, 12% ispunjeno), 1 (*a priori*, prospektivno planiranje istraživanja, 35% ispunjeno) i 10 (procjena pristranosti u publiciranju, 40% ispunjeno).

Ista procjena ponovljena je pomoću R-AMSTAR ljestvice i dobiveni su sljedeći rezultati: najbolje čestice bile su 3 (sveobuhvatno pretraživanje literature, 86% studija s 4 boda) i 2 (dvostruki probir i ekstrakcija podataka, 62% studija s 4 boda), a najgore 10 (procjena pristranosti u publiciranju, 49% studija s 1 bodom) i 8 (znanstvena kvaliteta uključenih studija primjereno korištena u oblikovanju zaključaka, 44% studija s 1 bodom).

Usporedba metodološke kvalitete Cochraneovih i ostalih sustavnih pregleda

Cochraneovi sustavni pregledi (n=31) bili su kvalitetniji od onih koji nisu rađeni prema Cochraneovoj metodologiji (n=66), neovisno je li za procjenu korištena ljestvica AMSTAR ili R-AMSTAR. Medijan bodova koji su dodijeljeni Cochraneovim sustavnim pregledima iznosio je 9 (IQR: 8-10) od 11 mogućih na AMSTAR ljestvici i 37 (IQR: 33-40) od moguća 44 boda na R-AMSTAR ljestvici. Ostali sustavni pregledi imali su medijan 6 (IQR: 5-7) bodova na AMSTAR ljestvici i 29 (IQR: 25-32) od moguća 44 boda na R-AMSTAR ljestvici. Slična razlika u metodološkoj kvaliteti nađena je pretvorbom zbroja bodova pojedinih ljestvica u percentile [AMSTAR: Cochraneovi medijan (IQR): 80,93 (71,13-90,72) vs. ostali medijan (IQR): 47,94 (27,84-61,86); percentili R-AMSTAR: Cochraneovi medijan (IQR): 83 (61,3-92,15) vs. ostali medijan (IQR): 42,3 (20,1-57,7)].

Podudarnost ocjenjivača

Razina podudarnosti među dva neovisna ocjenjivača bila je u rasponu od loše (Gwetov AC1 <0) do skoro savršene (Gwetov AC1 0,81–0,99) podudarnosti za pojedinu česticu. Sveukupni koeficijent podudarnosti za sve čestice bio je značajan za AMSTAR (Gwetov AC1=0,62, 95%CI 0,39-0,86) i R-AMSTAR (Gwetov AC1=0,62, 95%CI 0,53-0,70).

3.4.4 Rad 4. Istraživanje primjerenosti ključnih domena ishoda i mjera ishoda IMMPACT inicijative među autorima sustavnih pregleda o intervencijama za ublažavanje neuropatske boli

Ispitanici

Od 283 poslana poziva na sudjelovanje u istraživanju, 19 nije moglo biti isporučeno na valjanu adresu elektroničke pošte. Iako je 39 (15%) kontaktiranih autora dalo informirani pristanak za sudjelovanje, njih 34 (13%) sudjelovalo je u istraživanju. Pet autora je odustalo od istraživanja nakon davanja informiranog pristanka, jedan autor odbio je sudjelovati nakon ispunjavanja općih podataka jer je smatrao da nema dovoljno znanja o istraživanom pitanju, a neki su autori odustajali u daljnjem tijeku istraživanja pa je ukupno 28 ispitanika ispunilo pitanja o ključnim domenama ishoda, a 25 o ključnim mjerama ishoda.

Većina sudionika bili su muškarci, kliničari, s više od 10 godina iskustva u liječenju kronične boli. Pet od 34 sudionika je sudjelovalo u razvijanju ključnog skupa ishoda za određeno područje (bilo IMMPACT ili druge organizacije). Polovina ispitanika (17/34) objavila je prospektivno protokol istraživanja sustavnog pregleda.

Ključne domene ishoda

Dvadesetčetiri od 33 (74%) ispitanika znalo je za IMMPACT ključni skup domena ishoda, a 16 od 20 sudionika (80%) znali su točan broj domena u ključnom skupu (ostali su preskočili pitanje). Skoro svi sudionici (27/28) su točno izabrali bol, tjelesno funkcioniranje i emocionalno funkcioniranje kao domene koje pripadaju IMMPACT-preporučenom ključnom skupu ishoda.

Ispitanici su zatim ocjenjivali važnost ponuđenih domena ishoda na ljestvici 1-9. Bol i tjelesno funkcioniranje ocijenilo je 26 od 28 (93%) sudionika kao domene ishoda od ključne važnosti (ocijenjeni ≥7). Konsenzus o uključenju domene ishoda u ključni skup postignut je za 5 od 6 postojećih IMMPACT ključnih domena ishoda (bol, tjelesno funkcioniranje, emocionalno funkcioniranje, ispitanikova ocjena poboljšanja i zadovoljstvo liječenjem, simptomi i nuspojave) i 1 dodatnu domenu (funkcioniranje u ulozi). Samo je 3 od 28 (11%) sudionika koristilo sve ključne domene ishoda, a 14 (50%) je koristilo dio ključnih domena ishoda prilikom pripremanja sustavnog pregleda, iako su ti sustavni pregledi objavljeni nakon IMMPACT preporuka. Najčešće navedeni razlozi zbog kojih ključne domena ishoda nisu bile korištene su: nedovoljno poznavanje IMMPACT preporuka (13/28), domene nisu bile

korištene u randomiziranim kontroliranim istraživanjima (12/28) i korištenje ključnog skupa ishoda nije bilo obvezno prilikom registracije protokola i/ili objavljivanja rada (11/28).

Ključne mjere ishoda

Većina sudionika (18/25) znala je za IMMPACT-preporučene ključne mjere ishoda za procjenu učinkovitosti i sigurnosti ispitivanih modaliteta liječenja kronične boli. Prilikom odabira mjera koje je IMMPACT inicijativa označila ključnima, 24 od 25 (96%) sudionika točno je odabralo ljestvicu PGIC, a 22 od 25 (88%) točno je odabralo 11-djelnu ljestvicu NRS. Autori sustavnih pregleda su najčešće pogrešno označili ljestvicu VAS kao ključnu mjeru ishoda IMMPACT inicijative. Zatim su ispitanici zamoljeni da ocijene važnost ponuđenih mjera ishoda na ljestvici 1-9: 23/25 (92%) ih je ocijenilo ljestvice PGIC, a 22/25 (88%) 11-djelnu ljestvicu NRS kao mjere ishoda od ključne važnosti (ocijenjene ≥7). Od ponuđenih ključnih mjera ishoda IMMPACT inicijative samo je za 2 ljestvice postignut konsenzus o uključenju u ključni skup mjera ishoda za procjenu učinkovitosti liječenja: PGIC i NRS.

Četiri od 24 (17%) sudionika čiji su sustavni pregledi objavljeni nakon 2005. (nakon IMMPACT preporuka) koristila su IMMPACT-preporučene ključne mjere ishoda tijekom izrade sustavnog pregleda, a 11 (46%) ih je koristilo te mjere djelomično. Najčešći razlozi zbog kojih ključne mjere ishoda koje preporučuje IMMPACT nisu bile korištene su: mjere ishoda nisu bile dostupne u randomiziranim kontroliranim istraživanjima (12/25) i korištenje ključnih mjera ishoda nije bilo obvezno prilikom registracije protokola i/ili objavljivanja rada (11/25). Mnogi su sudionici (10/25) naveli da su koristili druge mjere ishoda koje su smatrali primjerenijima svom istraživanju.

3.5 RASPRAVA

Najvažniji rezultati prvog rada, koji se temelji na 97 uključenih sustavnih pregleda randomiziranih kontroliranih pokusa, pokazuju da unatoč postojanju brojnih intervencija za liječenje neuropatske boli nedostaju dorečeni dokazi temeljeni na istraživanjima visoke kvalitete o učinkovitosti i sigurnosti većine istraživanih načina liječenja. Iako nađeni dokazi podržavaju učinkovitost određenih intervencija, većina zaključaka o učinkovitosti je nedorečeno ili nejasno. Nadalje, samo je jedan od osam zaključaka o sigurnosti istraživanih liječenja bio dorečen. Razlozi koji su sprječavali donošenje dorečenih zaključaka uglavnom su se odnosili na nisku kvalitetu ili nedostatak dostupnih dokaza. Ovo istraživanje prvi je provedeni sustavni pregled sustavnih preglednih radova o postojećim intervencijama za liječenje neuropatske boli. Znatna pažnja kliničara i istraživača usmjerava se ka poboljšanju ishoda liječenja bolesnika koji pate od neuropatske boli. To se odražava u sve većem broju objavljenih sustavnih pregleda na tu temu, a posebice činjenicom da je skoro pola sustavnih pregleda pronađenih u ovom istraživanju bilo objavljeno nakon 2011. Pritom valja uzeti u obzir da su sustavni pregledi relativno novi oblik istraživanja.

Većina dobivenih rezultata slaže se s preporukama NeuPSIG-a o farmakološkom liječenju neuropatske boli objavljenima 2015. Te preporuke predlažu TCA, inhibitore ponovne pohrane serotonina i noradrenalina, pregabalin i gabapentin kao prvu liniju liječenja periferne i centralne neuropatske boli. Lidokainski naljepak, topikalni kapsaicin visoke koncentracije (8%) i tramadol predlažu se kao druga linija liječenja, a jaki opioidi i botulinum toksin A kao treća linija liječenja. Topikalni pripravci i botulinum toksin A preporučeni su samo za perifernu neuropatsku bol. Kanabinoidi i valproat dobili su blagu, a levetiracetam i meksiletin snažnu preporuku protiv njihova korištenja u liječenju neuropatske boli zbog negativnih rezultata o učinkovitosti i nuspojava (5). Ostala istraživana liječenja (npr. karbamazepin, lamotrigin, selektivni inhibitori ponovne pohrane serotonina) ili kombinirano liječenje dobili su nedorečene preporuke zbog nedosljednih rezultata, iako neki od tih lijekova mogu biti učinkoviti u odabranoj podgrupi bolesnika (10). Smjernice NeuPSIG-a o intervencijskom (invazivnom) liječenju neuropatske boli objavljene su 2013. i sadrže uglavnom nedorečene preporuke zbog niske kvalitete dostupnih istraživanja. U njima se nalaze slabe preporuke za epiduralnu primjenu kortikosteroida zbog kratkotrajne dobrobiti u liječenju lumbalne radikulopatije, iako nije bilo dovoljno dokaza koji ukazuju na smanjenje boli dulje od 12

tjedana nakon njihove primjene, kao ni dokaza da smanjuju potrebu za kirurškim liječenjem (12), što se slaže s našim rezultatima.

Snaga prvog istraživanja počiva na uključenju raznih neuropatskih stanja, sveobuhvatnom pregledu učinkovitosti i sigurnosti postojećih modaliteta liječenja neuropatske boli, pridržavanju PRISMA smjernicama pri izradi istraživanja te uključenju sustavnih pregleda bez jezičnog ograničenja. Rezultati prvog istraživanja su pokazali da je većina sustavnih pregleda istraživala liječenje boli u bolesnika s nekoliko vrsta neuropatske boli (kao što su bolna dijabetička neuropatija, lumbalna radikularna bol i postherpetička neuralgija) unatoč postojanju mnogih tipova neuropatske boli. Nadalje, mnoge vrste liječenja nisu uključene jer nisu prošle strogu provjeru u randomiziranim kontroliranim istraživanjima, moguće zbog metodoloških i etičkih izazova u provođenju intervencijskih kliničkih istraživanja (12). Moguće je da postoje liječenja već istražena u randomiziranim kontroliranim istraživanjima, ali ih sustavni pregledni rad nije još istražio pa samim time nisu uključena u naš sustavni pregled sustavnih pregleda. Neka bolna stanja možda nisu uključena tijekom probira jer nisu samo neuropatska, već u njima postoji somatska komponenta boli (npr. bol u donjem dijelu leđa). Kriterij uključenja temeljio se na definiciji neuropatske boli IASP udruženja (24) što je dovelo do isključivanja mnogih sustavnih pregleda koji su u istraživanje uključili ispitanike s neuropatskom i ostalim vrstama boli koji ne odgovaraju IASP-ovoj definiciji neuropatske boli. Ograničenja ovih rezultata vezana su i za metodološke nedostatke uključenih sustavnih pregleda, nedostatno definiranje dijagnostičkih kriterija temeljem kojih su ispitanici uključeni u sustavne preglede, nepotpuno prijavljivanje trajanja liječenja i trajanja praćenja ispitanika, što ograničava primjenu rezultata u kliničkoj praksi. Nadalje, većina uključenih sustavnih pregleda nije obnavljana tijekom godina što znači da postoji mogućnost da sadrže zastarjele dokaze.

Drugo istraživanje pokazalo je nedovoljno korištenje ključnog skupa domena i mjera ishoda koje je preporučila inicijativa IMMPACT za procjenu učinkovitosti i sigurnosti liječenja u sustavnim pregledima o neuropatskoj boli. Uključeni sustavni pregledi koristili su medijan četiri od šest IMMPACT-preporučenih ključnih domena ishoda i medijan pet od sveukupno 11 domena ishoda. Samo 10% sustavnih pregleda koristilo je svih šest ključnih domena ishoda, a četvrtina tek jednu ili dvije ključne domene ishoda prema preporukama IMMPACT-a. Naši rezultati ukazuju na nedovoljno korištenje relevantnog preporučenog ključnog skupa domena ishoda za kroničnu bol u kohorti sustavnih pregleda o liječenju neuropatske boli. Od šest IMMPACT-ovih ključnih domena ishoda najčešće je korištena bol, što se slaže s

rezultatima jednog istraživanja o korištenju ishoda u liječenju neuropatske boli (28). Bol je najčešće procijenjena pomoću VAS i NRS ljestvica, a Verbalna ljestvica za bol (engl. *Verbal Rating Scale*,VRS) bila je na trećem mjestu najviše korištenih mjera za procjenu razine boli. Suprotno preporukama NeuPSIG-a koji preporučuje VAS ili NRS ljestvicu (a VRS kao sekundarnu mjeru ishoda) za procjenu razine boli (29), IMMPACT ne preporučuje korištenje VAS ljestvice (18). IMMPACT preporučuje 11-djelnu NRS ljestvicu kao ključnu mjeru ishoda, osim u stanjima za koja se rutinski koriste pouzdane i validirane mjere ishoda koje se ne temelje na NRS ljestvici ili kada je korištenje NRS ljestvice problematično, kada preporučuje VRS ljestvicu (18).

Dvije važne domene koje su dio IMMPACT-ovog ključnog skupa ishoda su nuspojave i dispozicija ispitanika, a korištene su u 84% (nuspojave) i 50% (dispozicija ispitanika) uključenih sustavnih pregleda. Niža stopa prijavljivanja pridržavanja liječenju i razloga za preuranjeno povlačenje iz istraživanja u sustavnim pregledima može biti posljedica njihova neprijavljivanja u randomiziranim kontroliranim istraživanjima.

Rezultati ovog istraživanja ukazuju na značajnu heterogenost u korištenju mjera ishoda za procjenu učinkovitosti i sigurnosti istraživanih intervencija za neuropatsku bol, što ograničava usporedbu rezultata različitih sustavnih pregleda. Standardizacija korištenja mjera ishoda može poboljšati usporedivost i kliničku primjenjivost rezultata kliničkih istraživanja o liječenju kronične boli (18).

Korištenje ključnog skupa ishoda u sustavnim pregledima je rijetko (30). Pokazano je da čak ni Cochraneovi sustavni pregledi, koji se izrađuju prema striktnoj metodologiji (31, 32), ne koriste ključni skup ishoda kao smjernice pri izboru istraživanih ishoda. Istraživanje o upotrebi ključnog skupa ishoda provedeno 2015. pokazalo je da niti jedan od 375 analiziranih sustavnih pregleda nije izričito naveo da su koristili ključni skup ishoda prilikom određivanja ishoda koje će izložiti u istraživanju, iako je moguće da su se koristili preporukama o ključnom skupu ishoda, ali ih nisu spomenuli (33). Rezultati ovog istraživanja potvrđuju taj rezultat: niti jedan sustavni pregled nije spomenuo preporuke IMMPACT inicijative za izbor ključnih ishoda za procjenu učinkovitosti i sigurnosti istraživanih intervencija za liječenje neuropatske boli.

Ograničenje ovog istraživanja vezano je za kategorizaciju ishoda u domene. Iako je provedeno dosljedno, svrstavanje korištenih ishoda nije jednostavno zbog postojećeg preklapanja nekih ishoda. Nadalje, uspoređivane su domene i mjere ishoda navedene u

metodama s onima prikazanima u rezultatima objavljenih sustavnih pregleda. Idealno bi bilo usporediti protokole sustavnih pregleda koji su objavljeni prije objavljivanja samog rada s rezultatima u objavljenom radu, ali to nije bilo omoguće napraviti jer je samo manji dio sustavnih pregleda imao *a priori* objavljen protokol. Sustavni pregledi koji se izrađuju unutar Cochranea imaju obvezu objavljivanja protokola u CDSR, a od 2011. omogućeno je i ostalim autorima sustavnih pregleda prospektivno registriranje protokola u PROSPERO registru (34). Moguće je da autori smatraju da neke od preporučenih ključnih domena ishoda nisu važne za pojedino istraživanje. U takvim slučajevima IMMPACT preporučuje navesti razloge isključenja određene ključne domene ishoda, ali mi takve primjere nismo našli među uključenim istraživanjima.

Pouzdanost rezultata sustavnih pregleda ovisi o kvaliteti uključenih randomiziranih studija, a isto tako pouzdanost rezultata sustavnog pregleda koji se temelji na sustavnim pregledima ovisi o kvaliteti uključenih sustavnih pregleda, što je istraženo u trećem radu. Sveukupna procjena metodološke kvalitete sustavnih pregleda o liječenju neuropatske boli uključenih u prvo istraživanje bila je osrednja, bez obzira je li metodološka kvaliteta procijenjena ljestvicom AMSTAR ili R-AMSTAR. Nekoliko ranijih istraživanja posvetilo se procjeni metodološke kvalitete sustavnih pregleda u drugim područjima boli pomoću AMSTAR ljestvice. Martinis i sur. procijenili su kvalitetu 40 sustavnih pregleda o kirurškom liječenju boli u lumbalnom dijelu leđa i našli su da je samo 5% sustavnih pregleda bilo visoke kvalitete, većina su bili osrednje, a 22,5% niske kvalitete (35). Istraživanje metodološke kvalitete 17 sustavnih pregleda o nefarmakološkom liječenju boli udružene s karcinomom Songa i sur. našlo je samo 1 visoko kvalitetni sustavni pregled u tom području, a 5 ih je bilo niske kvalitete. Srednji zbroj na AMSTAR ljestvici bio je 5,47 što označava umjerenu kvalitetu (36). Niti jedno istraživanje do sada nije istražilo metodološku kvalitetu sustavnih pregleda o boli pomoću R-AMSTAR ljestvice niti je usporedilo te dvije ljestvice.

Nedavno provedeni sustavni pregled Piepera i sur. istraživao je pouzdanost, vrijednost i izvodljivost ljestvica AMSTAR i R-AMSTAR te pokazao da AMSTAR ljestvica ima dobre mjerne osobitosti (jednostavno se primjenjuje, pouzdana i validirana ljestvica), dok ih R-AMSTAR nema (37). Autori su uključili 9 istraživanja koja su koristila AMSTAR, 2 koja su koristila R-AMSTAR i jedno koje je koristilo obje ljestvice. Pojedinosti o računanju razine podudarnosti među neovisnim ocjenjivačima nije bilo u istraživanjima koja su koristila R-AMSTAR (37). Obzirom na tu činjenicu i na rezultate istraživanja Wongpakarana i sur. koje je pokazalo da je Gwetov AC1 koeficijent stabilnija mjera podudarnosti među ocjenjivačima

od Cohenove Kappe u uzorku poremećaja osobnosti (38), odlučeno je u trećem istraživanju koristiti Gwetov AC1 koeficijent uz napomenu da je tumačenje mjera podudarnosti po Landisu i Kochu izvorno objavljeno za Cohenov Kappa koeficijent i možda nije potpuno primjenjivo za tumačenje AC1 koeficijenta jer su Gwetove AC1 vrijednosti veće nego Kappa vrijednosti (38).

Također je na uzorku sustavnih pregleda o liječenju neuropatske boli potvrđena viša kvaliteta sustavnih pregleda rađenih prema Cohraneovoj metodologiji, što je nekoliko prethodnih istraživanja u drugim područjima već pokazalo (31, 32, 39-41).

Ograničenje trećeg istraživanja je uključivanje sustavnih pregleda objavljenih od 1995. iako je AMSTAR ljestvica objavljena 2007.godine. Moguće je da je došlo do poboljšanja metodološke kvalitete sustavnih pregleda nakon objavljivanja AMSTAR ljestvice, a već postoje dokazi u prilog tome (42-45). Drugo ograničenje vezano je za način bodovanja AMSTAR čestica koji podrazumijeva da svaka čestica ima jednaku težinu. Ta pretpostavka bi mogla biti pogrešna jer sve čestice AMSTAR-a ne bi smjele imati istu metodološku vrijednost (40). Nadalje, moguće je da je iskustvo ocjenjivača utjecalo na razlike u koeficijentima podudarnosti među ocjenjivačima u našem i drugim istraživanjima (46), iako je teško procijeniti utjecaj tog čimbenika jer se iskustvo ocjenjivača ne navodi često u uključenim istraživanjima (37). Obje ljestvice mogu primijeniti ocjenjivači bez prethodnog iskustva u njihovu korištenju nakon pomne diskusije svake od čestica i kalibracijske vježbe prije procjene kvalitete, što je i učinjeno u trećem radu. Buduća istraživanja mogla bi dodatno koristiti i novi alat ROBIS objavljen 2016. za procjenu rizika pristranosti u sustavnim pregledima (47). Nakon završetka ovog istraživanja objavljena je nova inačica ljestvice AMSTAR koja se naziva AMSTAR 2, i koju je potrebno ispitati u budućim istraživanjima (48).

Četvrti rad pokušao je pružiti odgovor na pitanje proizašlo iz drugog rada: koji su razlozi zbog kojih se autori sustavnih pregleda o liječenju neuropatske boli ne pridržavaju IMMPACT-ovih preporuka za odabir ključnih domena ishoda i mjera ishoda za kroničnu bol. Većina autora sustavnih pregleda koji su sudjelovali u istraživanju znala je za ključne domene (16) IMMPACT inicijative kao i mjere ishoda (18) za procjenu učinkovitosti i sigurnosti ispitivanih modaliteta liječenja kronične boli. Konsenzus o uključenju domena ishoda u ključni skup postignut je za 5 od 6 postojećih IMMPACT ključnih domena ishoda (bol, tjelesno funkcioniranje, emocionalno funkcioniranje, ispitanikova ocjena poboljšanja i

zadovoljstvo liječenjem, simptomi i nuspojave), što znači da autori sustavnih pregleda smatraju postojeće domene ishoda važnima.

Unatoč tomu što ih smatraju važnima, tek više od polovine ispitanika koristilo je barem jedan od šest ključnih domena ishoda prilikom pripremanja sustavnih pregleda objavljenih nakon IMMPACT preporuka. Najčešće navedeni razlozi koji su onemogućili korištenje ključnih domena ishoda u sustavnim pregledima su nedovoljno poznavanje IMMPACT preporuka, nedostatak ključnih domena ishoda u randomiziranim kontroliranim istraživanjima i činjenica da korištenje ključnog skupa ishoda nije obvezno prilikom registracije protokola i/ili objavljivanja rada.

Definiranje ključnog skupa ishoda tek je prvi korak u postupku standardizacije ishoda. Važno je provjeriti koristi li se preporučeni ključni skup ishoda kako bi se ustanovilo jesu li predložene domene i mjere ishoda važne, treba li ih nadopuniti novim domenama i mjerama ishoda, je li postupak uvođenja bio uspješan i je li potrebno uključiti nove sudionike u razvoj ključnog skupa ishoda (20). Unatoč niskoj stopi odaziva ispitanika, što je ujedno i glavno ograničenje ovog istraživanja, ovaj se rad može koristiti kao pokazatelj za periodičku procjenu ključnih domena i mjera ishoda koje je predložila IMMPACT inicijativa.

3.6 ZNANSTVENI DOPRINOS OBJEDINJENIH RADOVA

Objedinjavanjem triju sekundarnih istraživanja te četvrtog, primarnog istraživanja stječe se potpunija slika o uvjerljivosti, potpunosti i kvaliteti dokaza o intervencijama za liječenje neuropatske boli do sada istraživanih u sustavnim pregledima. Opisana istraživanja pokazuju da su mnoge postojeće intervencije istražene na malom broju neuropatskih bolnih stanja. Pružanjem potpunije slike o postojećim intervencijama cilj je bio nadahnuti istraživače da preuzmu načine liječenja koji su se pokazali učinkovitima u jednom stanju i istraže ih u drugim neuropatskim bolnim stanjima.

Ovo istraživanje ukazalo je na područja s nedostatkom kvalitetnih i uvjerljivih dokaza, nedostatnost prijavljivanja simptoma i nuspojava istraživanih modaliteta liječenja te potrebu za korištenjem jasnih dijagnostičkih kriterija prilikom definiranja ispitivane populacije. Također je pokazalo da metodološka kvaliteta postojeće baze znanja o neuropatskoj boli nije optimalna, što bi se moglo popraviti uvođenjem obvezne procjene kvalitete prilikom registracije protokola sustavnog pregleda.

Rezultati istraživanja pokazali su veliku heterogenost korištenih mjera ishoda za procjenu učinkovitosti i sigurnosti istraživanih intervencija za neuropatsku bol. To ukazuje na moguću potrebu za izmjenom i dopunom postojećih preporučenih domena i mjera ishoda, kao i potrebu za definiranjem ključnog skupa ishoda koji bi bio specifičan za neuropatsku bol. Domene ishoda i mjere ishoda prikazane u rezultatima ove disertacije mogu poslužiti kao temelj za prijedlog specifičnih ključnih domena ishoda i mjera ishoda za neuropatsku bol.

Temeljem rezultata prikazanih u ovoj disertaciji mogu se osmisliti intervencije za dosljedno korištenje preporučenih ključnih domena i mjera ishoda. Time bi se omogućilo lakše uspoređivanje rezultata različitih istraživanja, olakšalo bi se provođenje sustavnih pregleda/meta-analiza zbog postojanja homogenih ishoda u primarnim studijama, pojednostavnila bi se procjena kliničke učinkovitosti ispitivanih intervencija, smanjile bi se pristranost zbog neprijavljivanja važnih ishoda i količina nedovoljno informativnih istraživanja.

3.7 KRATKI SAŽETAK NA ENGLESKOM JEZIKU (SUMMARY)

Interventions for neuropathic pain: the analysis of the best available evidence and methods of treatment assessment

Introduction: Numerous interventions for neuropathic pain (NeuP) are available, but its treatment remains unsatisfactory.

Methods: This doctoral thesis consists of 4 studies that i) systematically summarized evidence from systematic reviews (SRs) of randomized controlled trials (RCTs) on interventions for NeuP, ii) assessed outcome domains and measures used for the assessment of treatment efficacy and safety, iii) the methodological quality of included SRs, and iv) awareness and acceptability of Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)-recommended core outcome set (COS) and core outcome measures (COMs) for chronic pain among authors of SRs.

Results: The most common interventions in 97 included SRs were pharmacological (59%) and surgical (15%). The majority of analyzed SRs were of medium quality. More than 50% of conclusions from abstracts on efficacy and around 80% on safety were inconclusive. The included SRs reported a median 4 out of 6 IMMPACT core domains. Pain intensity was mostly assessed with VAS (n=59) and NRS (n=29) scales. Authors of NeuP SRs insufficiently use relevant recommended COS because they are not aware of or they find it irrelevant.

Conclusions: Evidence about interventions for NeuP is frequently inconclusive or completely lacking. The methodological quality of analyzed SRs in the field of NeuP was not optimal. Further work on the IMMPACT COS is needed, in terms of evaluating its adequacy and uptake among authors.

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4 ŽIVOTOPIS

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JEZICI	Hrvatski (materinji jezik) Engleski (C1) Njemački (B2) Talijanski (A2)

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5 PRESLIKE RADOVA OBJEDINJENIH U DISERTACIJI

5.1 PRVI RAD

Section Editor: **Honorio T. Benzon**

SYSTEMATIC REVIEW ARTICLE

CME

Interventions for Neuropathic Pain: An Overview of Systematic Reviews

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Numerous interventions for neuropathic pain (NeuP) are available, but its treatment remains unsatisfactory. We systematically summarized evidence from systematic reviews (SRs) of randomized controlled trials on interventions for NeuP. Five electronic databases were searched up to March 2015. Study quality was analyzed using A Measurement Tool to Assess Systematic Reviews. The most common interventions in 97 included SRs were pharmacologic (59%) and surgical (15%). The majority of analyzed SRs were of medium quality. More than 50% of conclusions from abstracts on efficacy and approximately 80% on safety were inconclusive. Effective interventions were described for painful diabetic neuropathy (pregabalin, gabapentin, certain tricyclic antidepressants [TCAs], opioids, antidepressants, and anticonvulsants), postherpetic neuralgia (gabapentin, pregabalin, certain TCAs, antidepressants and anticonvulsants, opioids, sodium valproate, topical capsaicin, and lidocaine), lumbar radicular pain (epidural corticosteroids, repetitive transcranial magnetic stimulation [rTMS], and discectomy), cervical radicular pain (rTMS), carpal tunnel syndrome (carpal tunnel release), cubital tunnel syndrome (simple decompression and ulnar nerve transposition), trigeminal neuralgia (carbamazepine, lamotrigine, and pimozide for refractory cases, rTMS), HIV-related neuropathy (topical capsaicin), and central NeuP (certain TCAs, pregabalin, cannabinoids, and rTMS). Evidence about interventions for NeuP is frequently inconclusive or completely lacking. New randomized controlled trials about interventions for NeuP are necessary; they should address safety and use clear diagnostic criteria. (Anesth Analg 2017;125:643–52)

Neuropathic pain (NeuP) has been estimated to affect between 5% and 10% of the general population.[1–3] This multifactorial condition can be difficult to manage, irrespective of the cause of the underlying disorder.[4,5] Therefore, it is considered a priority health issue by the International Association for the Study of Pain (IASP).[5]

During recent years, several evidence-based clinical recommendations summarized evidence from randomized controlled trials (RCTs) about pharmacologic interventions for NeuP.[4,6–8] They have highlighted weaknesses in the existing evidence base from clinical trials and sometimes came to discordant conclusions as a result of methodological differences in evidence assessment.[9] Additionally, nonpharmacologic interventions (surgical or other) are frequently used as an alternative or additional therapy on top of pharmacologic therapies, because some patients do not respond to pharmacologic treatments, obtain only partial pain relief, or experience intolerable adverse effects.[10,11] The latest guideline for the interventional management of NeuP published in 2013 by the IASP Neuropathic Pain Special Interest Group indicated that many interventions used to treat refractory NeuP are supported by weak evidence.[11] There is an increasing number of systematic reviews (SRs) that have investigated different treatment modalities of NeuP. However, their findings can be difficult to interpret, and their conclusions are often discordant and limited by the quality of the included studies as well as the quality of SRs.[9]

Overviews of SRs are review-derived products that provide an evidence map about research questions that have been addressed by SRs.[12] Such reviews are useful at the most practical level for providing a succinct summary of existing evidence from SRs for a busy clinician regarding interventions of particular conditions. Overviews of SRs can point out lack of clinical trials and SRs in relevant areas or evidence base with inconclusive results.[13]

We hypothesized that many treatments used for certain NeuP conditions have not been investigated in other types of NeuP and that the evidence about efficacy and safety of interventions for NeuP is inconsistent and insufficient. Being aware that the evidence is constantly accumulating worldwide, the aim of this study was to provide an overview of SRs that have summarized evidence from RCTs about efficacy and adverse events of pharmacologic and nonpharmacologic interventions for treating various NeuP conditions. By providing a big picture about the state of evidence across various NeuP conditions, our aim is to inspire clinical researchers to try some successful approaches that are proven to work in 1 condition in other NeuP conditions too.

METHODS

The study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (available on request).[14]

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Reprints will not be available from the authors.

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Study Protocol

A protocol for this overview of reviews was developed a priori and registered in the PROSPERO International Prospective Register of Systematic Reviews (No. CRD42015025831).

Eligibility Criteria

Types of Studies. We included full reports of SRs of RCTs and quasi-RCTs with parallel group or crossover design evaluating the efficacy and safety of interventions to relieve NeuP. Other types of SRs were excluded. For updated reviews, only the latest version was included.

Participants. Patients of any age presenting with NeuP according to the IASP definition[15] were eligible for inclusion. Studies that included patients with disorders that do not satisfy the current IASP criteria for NeuP such as fibromyalgia, complex regional pain syndrome (CRPS) type 1, low back pain without radicular pain, and atypical facial pain were excluded.[15]

Painful conditions that may be attributed to both neuropathic and nociceptive mechanisms (such as pain in multiple sclerosis, cancer-related pain, poststroke pain) were excluded unless study authors categorized it as neuropathic. Studies that included patients with a combination of NeuP and noneligible conditions were excluded.

Interventions and Comparators. Any therapeutic intervention and any comparator (placebo, sham, or active treatment) were eligible for inclusion. Treatments were divided into pharmacologic, surgical, interventional (defined as "invasive procedures involving delivery of drugs into targeted areas or ablation/modulation of targeted nerves"[11]), physical (physical therapy, eg, exercise, physical modalities, patient education), and psychologic.

Outcomes. Studies were included if they assessed pain intensity with or without any other outcome measure. Studies in which pain was assessed only as a composite score were excluded.

Literature Search

The following databases were searched: MEDLINE, Cochrane Database of Systematic Reviews, DARE, CINAHL, and PsycINFO from the earliest date to March 9, 2015. Initially, a comprehensive search strategy was developed for MEDLINE by using medical subject heading terms and text words for NeuP and specific neuropathic conditions and combining those results with text words for SR/meta-analysis. The search strategy for MEDLINE (available on request) was adapted for each database. There was no language or publication date restriction.

Screening

At the beginning of the selection process, a calibration exercise was conducted to ensure reliability in correctly selecting articles for inclusion. This exercise entailed screening an initial sample of the included titles and abstracts by 2 team members independently. The eligibility criteria were modified, as necessary, to optimize clarity. Subsequently, 2 reviewers (SD and AJK) independently screened the remainder of the search results for inclusion using a predefined relevance criteria form for all levels of screening (eg, title and abstract, full-text review of potentially relevant articles). Discrepancies were resolved by discussion and the involvement of a third reviewer (LP).

Data Extraction

Data extraction forms were piloted by all team members independently on a random sample of 5 articles using MS Excel software (Microsoft Inc, Redmond, WA). The data extraction forms were revised after this exercise, as necessary. Subsequently, reviewer pairs (MC, MB, KB, MM) independently read each article and extracted relevant data. Differences in extraction were resolved by the involvement of a third reviewer (SD). Data items included study characteristics (number of authors, publication date, language, country of authors' origin, databases searched, number of updates, number of included RCTs and participants, intervention and comparator, presence of meta-analysis, funding source, patient characteristics [population defined in inclusion criteria], description of the condition, diagnostic tools for the condition, duration of treatment and follow-up, and outcome results).

Data Synthesis

Literature search results and the extracted data were summarized descriptively. An in-depth analysis of included SRs was compiled and depicted in Supplemental Digital Content, Table, http://links.lww.com/AA/B949. Conclusion statements from the abstracts of SRs were categorized by 2 reviewers (AJK and SD), independently, using a modified categorization by Tricco et al,[113] as follows: positive, positive inconclusive, no evidence, no opinion, equal (for comparison of multiple interventions), equal inconclusive (for comparison of multiple interventions), negative, negative inconclusive, or unclear, more research is needed. A third reviewer (LP) verified the categorizations to ensure accuracy and disagreements were resolved through discussion. Favorable result was classified as positive (ie, effective and safe intervention was rated as positive and vice versa). The conclusion was categorized as inconclusive if the authors indicated that more studies were needed for confirming the results or that evidence was of low quality. A detailed description of conclusion categories is presented in Supplemental Digital Content, Table, http://links.lww.com/AA/B949. Conclusion statements of SRs that included participants with multiple NeuP conditions were separately presented unless authors provided a summarized conclusion statement. To facilitate the presentation of the results in a summary of evidence section, we assigned a summarized inconclusive grade to SRs that presented multiple conclusions for various interventions or different outcomes investigated if at least 1 of the conclusions was rated as unclear or inconclusive.

Assessment of the Methodological Quality of Included Reviews

The methodological quality of included reviews was independently assessed by 2 authors (NM and KV) using A Measurement Tool to Assess Systematic Reviews (AMSTAR) quality assessment tool.[114] Discrepancies were resolved by the third author (AJK).

RESULTS

Literature Search

The literature search resulted in 2412 titles and abstracts, of which 2070 were excluded (Figure). Of the 342 full texts retrieved and screened in duplicate, 245 articles

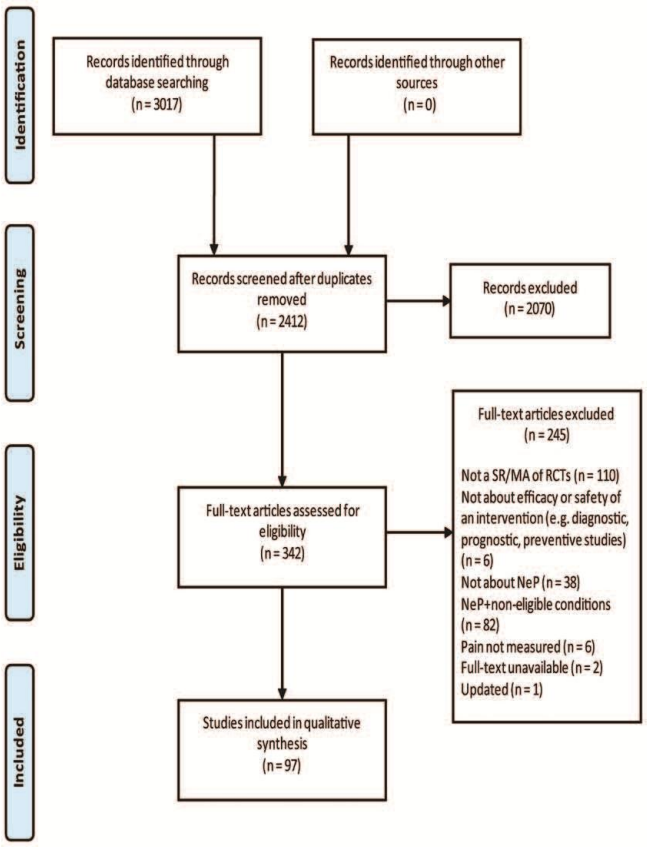

Figure. Study Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

were excluded (characteristics of the 245 excluded studies, with references, available on request). Ninety-seven SRs and/or meta-analyses of NeuP interventions were included in this overview of SRs: 65 with meta-analysis[16–20,22–25,28–35,37–51,54–57,59–62,65,67–69,71–79,83–86,90,92,94,96,97,99,101,103] and 32 without a meta-analysis.[21,26,27,36,52,53,58,63,64,66,70,80–82,87–89,91,93,95,98,100,102,104–112] Among those 32 SRs, 7 were empty with no studies included.[106–112]

Systematic Review Characteristics

The reviews were published between years 1995 and 2015 with nearly half (47%) published after 2011. Only 1 of 97 included SRs had a single author, and only 1 SR searched a single database, which is contrary to the SR methodology. Affiliations of authors of the included SRs were predominantly based in Europe (47%) and North America (20%). Forty-nine SRs included original studies published in any language. Only 6 SRs were published in languages other than English. The total number of included original RCTs was 1429. The number of RCTs included in each review ranged from 0 to 174, whereas 38% included between 2 and 10 studies. Approximately one third of SRs did not report the source of study funding. Only 10 SRs were updated, and 8 of them were published in the Cochrane Database of Systematic Reviews. Overall, approximately one fourth of Cochrane reviews were updated (8 of 31). A table with detailed characteristics of included studies is available on request.

Fifty-three SRs provided a detailed definition of the NeuP in the patient population under study, where most of the SRs studied painful diabetic neuropathy (PDN; 25%), lumbosacral radiculopathy (16%), or all types of NeuP (11%). Only 36 of the included SRs specified criteria for the diagnosis of painful neuropathic conditions that were investigated. A table with definitions and diagnostic criteria for NeuP used in the included studies is available on request.

The most common interventions were pharmacologic (59%) and surgical treatment (15%). Ten SRs that investigated more than 1 intervention most commonly included physical, interventional, and pharmacologic treatments (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

The duration of treatment across the included studies in SRs ranged from 2 minutes in the SR that investigated neurosurgical interventions (compared 2 techniques of radiofrequency thermocoagulation of the Gasserian ganglion) for the treatment of classical trigeminal neuralgia[89] to 36 months in the SR on the efficacy of aldose reductase

inhibitors in diabetic polyneuropathy.[28] The duration of follow-up ranged from 45 minutes in the SR that investigated pharmacologic interventions (ketamine infusion) for treating phantom limb pain[92] to 74 months in the SR on neurosurgical interventions (conventional radiofrequency thermocoagulation) for the treatment of classic trigeminal neuralgia.[89] Among 90 SRs with included RCTs, 26 did not report the length of treatment (2 studies stated that information was not provided in included RCTs); 22 did not report the duration of follow-up, and 4 of those 22 SRs indicated that follow-up time was not stated in original studies.

A total of 12 types of treatment comparisons were analyzed in the 97 included SRs. These comparisons were (1) pharmacologic versus placebo/sham[16–29,43–46,48,50,60,85,90,94–97,99–101]; (2) pharmacologic versus multiple interventions[31–33,36–40,49,51,52,68,87,92,98,102–105,107,108,111,112]; (3) pharmacologic versus pharmacologic[30,34,35,86]; (4) surgical versus surgical[59,61–63,73–77,83,84,89]; (5) surgical versus multiple interventions[64,78,110]; (6) multiple interventions versus multiple interventions[47,53,54,69–72,82,93,106]; (7) physical versus multiple interventions[42,55,79,80,109]; (8) physical versus placebo/sham[41,57,81]; (9) physical versus pharmacologic[88]; (10) interventional management versus multiple interventions[56,58,65,66]; (11) interventional management versus placebo/sham[67]; and (12) psychologic versus placebo/sham.[91] Detailed description of interventions and comparators is available in Supplemental Digital Content, Table, http://links.lww.com/AA/B949.

Methodological Quality of the Evidence

Overall, the analyzed SRs were of medium quality (median AMSTAR score, 6; range, 2–11 points). There were 34% SRs of high quality with an AMSTAR score of ≥8 of maximum 11 points, 57% SRs rated as medium quality with an AMSTAR score between 4 and 7, and 9% SRs rated as low quality with an AMSTAR score between 0 and 3. AMSTAR scores of each SR are presented in Supplemental Digital Content, Table, http://links.lww.com/AA/B949.

Studied Pharmacologic Treatments

Fifty-seven SRs examined pharmacologic treatment, of which 41 performed meta-analyses. Approximately half of the studies compared pharmacologic therapy with placebo. The authors investigated >1 medication in 20 SRs. Among SRs that studied a single drug class, anticonvulsants were most commonly represented (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Studied Surgical Treatments

Of 15 SRs that examined surgical treatments, 11 had meta-analyses. Surgical interventions were compared with another surgical technique in 12 of those SRs. The most commonly studied surgical interventions were different techniques of carpal tunnel release and discectomy for lumbosacral radiculopathy (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Other Studied Treatments

The remaining 25 SRs studied multiple interventions such as physical, interventional, and psychologic treatment modalities (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Ten SRs examined and compared >1 intervention, of which half performed a meta-analysis. Conditions studied, interventions, and comparators are heterogeneous and presented in Supplemental Digital Content, Table, http://links.lww.com/AA/B949.

Five SRs with and 4 without a meta-analysis studied physical treatment modalities, most commonly transcutaneous electrical nerve stimulation and acupuncture. The treatments were compared with multiple interventions in 5, sham treatment in 3, and pharmacologic treatment in 1 SR (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Interventional treatments were investigated in 5 SRs. The interventions included different approaches of epidural steroid injections for lumbosacral radiculopathy compared with epidural saline or local anesthetic injections and pharmacologic therapy (Supplemental Digital Content, Table, http://links.lww.com/AA/B949). Three of these SRs included a meta-analysis.

Mirror therapy for phantom limb pain compared with placebo was the only psychologic intervention studied (Supplemental Digital Content, Table, http://links.lww.com/AA/B949) in a SR without a meta-analysis.

Conclusiveness of Evidence

To facilitate the summary and comparison of a large number of reviews, we have evaluated conclusions of included studies regarding efficacy and safety using multiple categories related to their conclusiveness. Because several included studies investigated multiple conditions or interventions, the total number of conclusion statements is higher than the number of included studies (116 for efficacy and 115 for safety).

Overall, we found that 54% (63 of 116) conclusion statements were unclear, inconclusive, or without the opinion about the efficacy of analyzed interventions. Positive or equally effective opinion on the efficacy was provided in approximately one third of conclusions (36% [42 of 116]), and only 3% of the conclusions were negative (4 of 116). There was no evidence of efficacy for 7 investigated interventions (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Safety, on the other hand, was not mentioned, inconclusive, or unclear in 94 of 115 analyzed conclusions. The reviewers judged interventions as safe or equally safe as comparators in 8 of 115 (7%) and as unsafe in 6 of 115 (5%) conclusion statements. For 7 interventions, the authors indicated that there was a lack of available evidence to make conclusions about safety (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

SUMMARY OF EVIDENCE

Painful Diabetic Neuropathy

Among 27 SRs on PDN, only 9 indicated conclusive evidence about the efficacy of analyzed interventions. Positive conclusive evidence was reported for pregabalin,[16–18] topiramate and oxcarbazepine,[18] opioids,[25] and gabapentin.[37] Negative conclusive evidence was reported for aldose reductase inhibitors.[28] Three studies compared multiple drug classes and reported conclusive evidence of therapeutic equivalence of antidepressants and anticonvulsants, selective serotonin reuptake inhibitors and tricyclic antidepressants (TCAs), gabapentin, and older anticonvulsants (phenytoin and carbamazepine)[24]; gabapentin and TCAs[40];

and 29 drugs analyzed (with best results on a 100-point visual analog scale and 11-point numeric rating scale for pregabalin ≥300 mg and sodium valproate, respectively).[38]

Regarding the safety of interventions for PDN, only 3 studies appeared conclusive. Conclusive positive results were reported for pregabalin,[16] equal for antidepressants and anticonvulsants for minor adverse effects, but negative for discontinuation of antidepressants[24] and negative for amitriptyline.[37] Most of the studies did not provide any opinion on the safety of analyzed interventions in their conclusions (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Postherpetic Neuralgia

Of 16 SRs that investigated various interventions in postherpetic neuralgia (PHN), half presented positive conclusive evidence about the efficacy of gabapentin,[43–45] opioids,[25] high-concentration topical capsaicin,[46] TCAs,[47] and multiple pharmacologic treatments.[48,49] In addition, 2 SRs reported conclusive evidence of equal efficacy of antidepressants and anticonvulsants[24] and gabapentin and TCAs.[40] Safety was not mentioned or it was reported as inconclusive in the majority of SRs (13 of 16). Gabapentin was rated as safe in 2 studies[43,44] (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Lumbar Radicular Pain

Lumbar radicular pain management was addressed in 17 SRs; 12 reported inconclusive evidence on efficacy and 15 inconclusive evidence on the safety of different conservative and surgical interventions. Epidural corticosteroids[56,58] and repetitive transcranial magnetic stimulation (rTMS)[57] were conclusively shown to be effective. Only 4 of 10 studies on epidural corticosteroid injections analyzed radicular and axial pain scores separately.[58,67,68,71] Evidence was presented as conclusive on minimally invasive discectomy, which was equally effective and safe as open discectomy.[59] One SR[60] reported negative conclusive evidence on efficacy and safety of systemic steroids and advised against their use (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Cervical Radicular Pain

Only 2 SRs analyzed the management of cervical radicular pain. Evidence on the efficacy was presented as positive conclusive for rTMS.[57] Efficacy of conservative treatment (mechanical traction, physiotherapy, cervical collar, manual therapy, exercise, or their combination) was rated as inconclusive as a result of low or very low quality of evidence, although some modalities showed promising results (collar or physiotherapy at short-term follow-up were more effective on neck and arm pain than a wait-and-see policy).[72] Neither of the 2 SRs provided an opinion regarding the safety of the studied interventions (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Compressive Neuropathies (Carpal and Cubital Tunnel Syndrome)

We included 10 studies that analyzed different surgical and conservative interventions for carpal tunnel syndrome. Of 6 SRs that investigated surgical techniques, 3 presented conclusive evidence on their efficacy: 1 SR[73] presented evidence of equal efficacy of standard open carpal tunnel release to alternative surgical procedures and the other 2 SRs[74,75] provided equal or positive conclusions for open versus endoscopic carpal tunnel release for different outcomes studied. Therapeutic ultrasound,[79] oral steroids, splinting, ultrasound, yoga, and carpal bone mobilization among nonsurgical treatments analyzed[82] showed positive but inconclusive results. Ergonomic keyboard[81] and exercise and mobilization interventions[80] were conservative treatments with unclear efficacy.

The evidence of safety was judged as conclusive in half of SRs on surgical interventions but in none of the SRs on conservative interventions. Endoscopic carpal tunnel release appeared to be safer than the open release in 1 study.[74] However, other 2 studies[75,76] stated that this procedure increases the risk of reversible nerve injury compared with open carpal tunnel release (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Regarding the evidence on cubital tunnel syndrome, both studies[83,84] conclusively showed that simple decompression and ulnar nerve transposition were equally effective, but provided no opinion regarding their safety (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Trigeminal Neuralgia

Six SRs investigated treatments for trigeminal neuralgia. Conclusive evidence on efficacy for trigeminal neuralgia was presented for rTMS[57] and carbamazepine.[85] Lamotrigine and pimozide were positively rated for refractory trigeminal neuralgia.[85] Other 4 SRs had inconclusive (carbamazepine compared with topiramate,[86] tizanidine, pimozide,[87] and acupuncture[88]; 0.5% proparacaine hydrochloride compared with placebo[87]) or unclear statements in their conclusions (neurosurgical interventions: peripheral interventions, percutaneous interventions applied to the Gasserian ganglion, and 2 modalities of stereotactic radiosurgery[89]).

Safety of analyzed interventions was either not mentioned or presented as inconclusive in all SRs (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

HIV-Related Neuropathy

Various pharmacologic interventions for HIV-related neuropathy were compared in 4 SRs. Three SRs presented conclusive evidence on the efficacy of 8% capsaicin.[46,49,90] One study did not recommend smoked cannabis as a routine treatment,[90] and evidence was inconclusive in another study.[48] None of the studies provided conclusive statements regarding the safety of interventions studied (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Phantom Limb Pain

We found inconclusive evidence from 2 SRs that investigated the analgesic efficacy and safety of mirror therapy[91] and different drug classes (*N*-methyl-D-aspartate receptor antagonists, antidepressants, anticonvulsants, local anesthetics, opioids, and calcitonin)[92] in the management of phantom limb pain. Morphine, gabapentin, and ketamine showed trends toward short-term benefit, whereas memantine and amitriptyline did not provide pain relief[92] (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Other Peripheral Neuropathic Pain Conditions

Two SRs analyzing interventions for other peripheral NeuP conditions had inconclusive efficacy statements. One

study analyzed surgical and nonsurgical interventions for Morton's neuroma,[93] and the other studied pregabalin and gabapentin for posttraumatic pain.[48]

Two studies presented positive conclusive evidence about the efficacy of rTMS[57] in painful peripheral neuropathy and some of the studied drug classes for painful polyneuropathy and mixed NeuP[49] (Supplemental Digital Content, Table, http://links.lww.com/AA/B949). Safety was not addressed in conclusions of any of those 4 studies.

Central Neuropathic Pain

We did not find conclusive evidence of the efficacy of pharmacologic interventions studied in spinal cord injury-related pain[94,95] and multiple sclerosis-related pain.[48] Two studies that included participants with various central NeuP conditions suggested TCAs, pregabalin, and cannabinoids[49] as well as rTMS[57] as interventions with conclusive efficacy. Safety was not addressed in 4 and was rated as inconclusive in 1 study[94] (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

Multiple Neuropathic Pain Conditions

Eight SRs that included participants with multiple NeuP conditions presented unclear or inconclusive evidence about the efficacy of different pharmacologic interventions studied. Conclusive efficacy was described for low- and high-concentration topical capsaicin,[96] pregabalin, and duloxetine.[97] One study advised against the use of nortriptyline as a first-line treatment.[98] None of the studies provided clear statements regarding the safety of the analyzed treatments (Supplemental Digital Content, Table, http://links.lww.com/AA/B949).

DISCUSSION

The major findings of this overview, based on 97 SRs involving 1429 original RCTs, demonstrate that although a large number of therapeutic approaches have been proposed for the treatment of NeuP, there is a lack of conclusive evidence from high-quality SRs evaluating the efficacy and safety of most of the investigated treatments. While presented evidence supports the efficacy of some interventions, the majority (54%) of conclusions are inconclusive or unclear. Furthermore, we found that only 1 in 8 conclusion statements had a conclusive tone when addressing the safety of analyzed interventions. Conclusive recommendations could not be made mostly as a result of the lack or the poor quality of available data.

To our best knowledge, this is the first overview of SRs about interventions for NeuP. Improving therapy for patients with NeuP is attracting considerable attention of clinicians and researchers worldwide. Increasing numbers of original studies and SRs about NeuP are being published. Although the search strategy was not restricted by publication date, we found SRs published only within the past 20 years with nearly half of them published after the year 2011. This is understandable, considering that SRs are a relatively new form of research.

Methodological Quality and Main Findings of Systematic Reviews

Reliability of results in SRs depends on the quality of included studies and their conclusions. Likewise, the validity of results in an overview of SRs depends on the quality of included SRs. Therefore, we used the AMSTAR assessment tool to analyze the methodological quality of included SRs. Overall, most of the included SRs were of medium quality.

High-Quality Evidence

There is evidence from high-quality SRs that opioids were superior to placebo,[25] and gabapentin and TCAs were equally effective[40] for managing pain in diabetic neuropathy and PHN. High-concentration topical capsaicin was effective in PHN and HIV-related neuropathy.[46] Aldose reductase inhibitors were ineffective[28] for managing pain in diabetic neuropathy. Another review found little evidence to support the use of nortriptyline to treat several NeuP conditions.[98] Studies on surgical treatment of compressive neuropathies (carpal[73] and cubital tunnel syndrome[84]) showed similar symptom relief for different surgical techniques.

Medium-Quality Evidence

Compared with placebo, pregabalin,[16–18] topiramate, and oxcarbazepine[18] were superior in reducing pain in diabetic neuropathy. Good efficacy in PHN was reported for pregabalin, topical capsaicin, opioids,[48,49] gabapentin,[43–45,48,49] TCAs,[47–49] lidocaine plasters,[48] and sodium valproate.[49] Pregabalin and duloxetine had the largest beneficial effects for chronic peripheral NeuP.[97] Carbamazepine was found to be the drug of choice for trigeminal neuralgia.[85] High-concentration topical capsaicin was suggested to provide pain relief in HIV-related neuropathy,[49,90] and smoked cannabis was not recommended as a routine therapy.[90] Epidural administration of corticosteroids was effective in the management of lumbar radicular pain,[56,58] minimally invasive discectomy and open discectomy were equal in pain relief and rate of total complications,[59] and systemic steroids received recommendation against their use because of the lack of their efficacy.[60] Discrepant conclusions for different outcomes studied came from SRs that compared endoscopic and open carpal tunnel release.[74–76] Simple decompression of the ulnar nerve was as effective as anterior transposition for the surgical treatment of ulnar nerve compression.[83] Positive effects of TCAs, pregabalin, and cannabinoids[49] were suggested for managing central NeuP.

Low-Quality Evidence

Based on low-quality studies, gabapentin[37] was better than placebo in diabetic neuropathy, and antidepressants and anticonvulsants were equally effective for reducing pain in diabetic neuropathy and PHN, although patients are less likely to stop taking anticonvulsants as a result of adverse effects.[24] Conclusive efficacy was described for low- and high-concentration topical capsaicin[96] for peripheral NeuP conditions. rTMS appeared effective in lumbar and cervical radicular pain, trigeminal neuralgia, peripheral nerve pain, and central NeuP.[57]

No Evidence

Seven SRs were so-called empty reviews, ie, they had no RCTs included. This indicates topics that require immediate attention of researchers: decompressive surgery of lower limbs for symmetric PDN,[110] drug therapy for chronic idiopathic axonal polyneuropathy,[111] immunosuppressive treatment for nonsystemic vasculitic neuropathy,[107] immunotherapy for idiopathic lumbosacral plexopathy,[108] transcutaneous

electrical nerve stimulation for phantom pain and stump pain after amputation in adults,[109] immunotherapy for diabetic amyotrophy,[112] and treatment for idiopathic and hereditary neuralgic amyotrophy (brachial neuritis).[106]

Comparison With the Existing Literature

The majority of our findings are in agreement with IASP Special Interest Group on Neuropathic Pain (NeuPSIG) evidence-based recommendations for pharmacotherapy of NeuP from 2015, which proposed TCAs, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin as first-line treatment for peripheral or central NeuP; lidocaine patches, capsaicin high-concentration (8%) patches, and tramadol as second line; and strong opioids and botulinum toxin A as third line. Topical agents and botulinum toxin A were only recommended for peripheral NeuP. Cannabinoids and valproate received weak recommendations and levetiracetam and mexiletine received strong recommendations against their use in NeuP because of negative trial results or safety concerns.[4] Other drug treatments (eg, carbamazepine, lamotrigine, zonisamide, selective serotonin reuptake inhibitor antidepressants, topical treatments, and *N*-methyl-D-aspartate antagonists) or combination therapy received inconclusive recommendations because of generally discrepant findings, although some of these drugs might be effective in subgroups of patients.[9]

NeuPSIG recommendations for interventional management of NeuP published in 2013 were mostly inconclusive as a result of the poor quality of available of data. Weak recommendations were made for the use of epidural steroid injection for short-term benefits in lumbar radiculopathy, although there was insufficient evidence regarding pain relief beyond 12 weeks or for their use as surgery-sparing intervention,[11] which is in accordance with our findings.

Study Strengths and Limitations

Strengths of our study are the inclusion of various NeuP conditions, comprehensive overview of efficacy and safety of various treatment modalities for NeuP, the use of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement in conducting the overview as well as the inclusion of studies published in any language.

Our study showed that most SRs have focused on the management of pain in patients with few NeuP conditions, including PDN, lumbar radicular pain, and PHN, despite the existence of many NeuP types. This is related to the small prevalence of many NeuP conditions and difficulties in diagnosis. Additionally, many treatment modalities available were not included in our study because they have not undergone rigorous testing in well-designed RCTs, in some cases as a result of methodological and ethical challenges of conducting interventional clinical trials.[11] There may be interventions for NeuP that were investigated in RCTs but not yet addressed in an SR, and therefore, such interventions would not be covered with this overview. Also, there may exist relevant studies that were not touted as SRs or meta-analyses, and therefore, we may have missed them in our screening process. Some pain conditions may have been missed because they may exist in combination with somatic/non-NeuP generators.

During the previous 2 decades of research included in this overview, there have been changes in proposed NeuP definition. In 2008, NeuPSIG proposed a new definition of NeuP.[115] Based on the proposal of the IASP Taxonomy Committee, IASP accepted a somewhat modified version indicating NeuP is "pain caused by a lesion or disease of the somatosensory nervous system."[15] Our main inclusion criterion was based on that definition, in which we followed the recommendations of the IASP.[15] This led to the exclusion of multiple SRs where it was explicitly clear that the SR included studies in which patients with non-NeuP conditions were included.

Another important chronic pain condition, CRPS has not been included in this overview. According to the IASP diagnostic criteria to which we adhered, in CRPS type I, peripheral nerve injury cannot be identified, and only type II (CRPS-II) is considered to fall into a category of NeuP.[115,116] Potentially eligible reviews that included CRPS-II were excluded from our overview because they did not analyze CRPS-II separately. We did not use modified diagnostic criteria for CRPS ("Budapest criteria"),[117] because we tried to differentiate between neuropathic and nonneuropathic conditions. CRPS has been a topic of a recent Cochrane overview of SRs. Their study included 6 Cochrane and 13 non-Cochrane SRs, with a conclusion that there is a critical lack of high-quality evidence for the effectiveness of most analyzed therapies for the CRPS and that formulating an evidence-based approach to treatment of CRPS will remain difficult until further larger trials are undertaken.[118]

Limitations of the evidence found in this overview also include issues related to methodology, poor reporting, and the definition of NeuP. Among 97 studies, 1 SR had a single author, and 1 SR analyzed only 1 database. The methodology is what makes this kind of literature review "systematic"—first, it is necessary to involve >1 author for independent conduct of multiple methodological steps, and second, it is necessary to search >1 database to capture more relevant studies. When we consider these methodological requirements, reviews with a single author and single database search should not be considered systematic at all.

We also found multiple reporting deficiencies, namely the lack of specifying the detailed definition of NeuP and diagnostic criteria in the studied population as well as the omission of information on the duration of treatment and follow-up. This lack of information limits the usefulness of the SRs for clinical practice. The major limitation is also related to the lack of safety information for many of the investigated interventions, what could be the result of the lack of safety outcomes in primary studies. Furthermore, most of the SRs were not updated and therefore may represent outdated evidence.

It also has to be emphasized that our attempt to divide treatments into distinct categories is not straightforward because certain treatments do not fall easily into strict categorization.

CONCLUSIONS

Evidence from SRs about interventions for NeuP is frequently inconclusive or completely lacking. RCTs about interventions for NeuP should address open questions regarding the efficacy of treatments, analyze safety outcomes, study more head-to-head comparisons, study unexplored treatment modalities, and use clear diagnostic criteria, as specified by the IASP. Methodological quality of SRs about NeuP is not satisfactory. Future SRs should adhere to high methodological

and reporting standards and provide clear conclusions about both efficacy and safety of analyzed interventions.

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DISCLOSURES

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5.2 DRUGI RAD

Efficacy and Safety Outcome Domains and Outcome Measures in Systematic Reviews of Neuropathic Pain Conditions

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Objectives: Heterogeneity of outcome domains, used in interventional trials and systematic reviews (SRs) for neuropathic pain (NeuP), makes decisions on the comparative effectiveness of available treatments difficult. This study analyzed outcome domains and measures used in SRs of randomized controlled trials on efficacy and safety of interventions for NeuP and compared them with the core outcome set (COS) and core outcome measures (COMs) for chronic pain recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).

Methods: Five electronic databases were searched to find SRs of interventions for NeuP. Outcome domains and measures were independently extracted by 2 authors, and compared against the IMMPACT-recommended COS and COMs. Outcome domains specified in the methods and reported in the results were also compared.

Results: Ninety-seven SRs were analyzed. The 2 core domains most frequently specified in the methods and reported in the results of SRs were pain and symptoms and adverse events. Pain intensity was mostly assessed with Visual Analog Scale (n = 59) and Numerical Rating Scale (n = 29). The incidence (n = 70) and severity (n = 60) were most commonly reported for adverse events. There were 240 different outcome measures used for the assessment of treatment efficacy and safety.

Conclusions: Authors of SRs in the field of NeuP insufficiently use relevant recommended COS and COMs for chronic pain. More effort should be put into the implementation of COS to ensure that the study results can be compared and combined. There is a need for defining core outcome domains and measures specific for NeuP.

Key Words: neuropathic pain, systematic review, core outcome set, outcome measures, IMMPACT

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Heterogeneity of outcomes, used in interventional trials, systematic reviews (SRs), and meta-analyses (MA) for neuropathic pain (NeuP), can make decisions on comparative effectiveness of available NeuP treatments very difficult. For this purpose, the use of the core outcome set (COS) in specific research fields has been recommended. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative defines COS as an agreed minimum outcome set that should be measured and reported in all clinical trials conducted about a specific condition in order to facilitate comparing, contrasting, and combining of trial results. A COS is usually developed by a group of key relevant stakeholders, including patients and the public, health care professionals, and decision-makers in health, who need to make sure that the recommended outcomes will be relevant and important, and that they will influence policy and practice.[1]

Defining a COS is the first step in the process. As a specific COS is developed, the appropriate instruments that should be used for the assessment of the outcomes in a COS, (Core Outcome Measurement Instrument Sets) need to be established as well.[2]

Outcome standardization has been present in the clinical trials in rheumatology since the Outcome Measures in Rheumatology (OMERACT) initiative has recommended the relevant COS for osteoarthritis in 1997.[3] Since then, increased awareness about the importance of COS has contributed to its rapid development. A 2014 SR of Gargon et al found 198 COS in the literature, which were described in 250 publications.[4] Updated findings from the same research group, published in 2016, found 249 published COS.[5,6]

A COS that is relevant in the field of chronic pain was proposed in 2003 by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[7]

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L.P. conceived the study design and helped to resolve discrepancies in study selection process. A.J.K. and S.D. independently screened and included eligible studies. M.J., M.B., and D.M. performed the data extraction, and K.V. resolved discrepancies with the help of SD. S.D. performed data analyses and drafted the manuscript with the help of L.P.

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to be included in clinical trials. According to IMMPACT, the following 6 core outcome domains should be considered when designing chronic pain trials: (1) pain, (2) physical functioning, (3) emotional functioning, (4) participant ratings of improvement and satisfaction with treatment, (5) symptoms and adverse events, and (6) participant disposition.[7]

Supplemental outcome domains (clinician or surrogate ratings of global improvement, role functioning, pharmacoeconomic measures, biological markers) were also proposed. It was noted that core domains should be supplemented by any additional outcomes deemed relevant to a specific treatment.[7] The IMMPACT initiative has also recommended relevant outcome measures for the assessment of the outcomes in a COS for chronic pain trials 2 years after the introduction of core outcome domains.[8]

A previous study about outcome measures used in SRs of randomized controlled trials (RCTs) of NeuP conditions compared reported outcome domains with the COS recommended by the IMMPACT. The study analyzed 46 SRs published by January 2012 and reported outcome measures used for 4 of 6 core domains (pain intensity, physical functioning, emotional functioning, and participant ratings of improvement).[9] Mehta et al[9] found that those SRs were focused almost exclusively on pain intensity and much less on other 3 core outcome domains recommended for NeuP. That study did not investigate 2 relevant domains from the COS (symptoms and adverse events; and participant disposition), nor the reporting of supplemental IMMPACT domains and other specific outcomes and outcome measures used in NeuP trials. The adequate reporting of symptoms and adverse events, as well as participant disposition, is an important component of all trials and is essential for judging trials' efficacy and safety.[8]

Contributions to increased waste will continue to be made if relevant COS is not used in clinical trials and SRs on the subject.[10] Therefore, the aim of this study was to make a comprehensive analysis of both efficacy and safety outcome domains and outcome measures used in SRs of RCTs of interventions for NeuP. Outcome domains and measures used were compared with the core set of outcome domains (COS) and core outcome measures (COMs) recommended by the IMMPACT initiative for chronic pain trials. Additional goals were to compare outcome domains specified in the methods with those reported in the results of NeuP SRs and to investigate whether reporting of the IMMPACT-recommended outcomes improved over time.

METHODS

Study Design

First, a systematic literature search was performed to identify all published intervention SRs and/or MAs in NeuP that included defined efficacy and/or safety outcome domains and outcome measures. An a priori protocol for the overview of the SRs was developed and registered (PROSPERO, registration number: CRD42015025833). Subsequently, cross-sectional methodological analyses of outcome domains and outcome measures from those NeuP SRs were conducted.

Literature Search, Screening, and SR Inclusion

Five electronic databases were searched, including MEDLINE, Cochrane Database of Systematic Reviews, DARE, CINAHL, and PsycINFO, from the earliest date of database inception to March 9, 2015, without language restrictions. Search results were exported into the EndNote X5 software[11] and duplicates were removed. Titles and abstracts were screened independently by 2 authors (A.J.K., S.D.) and subsequently, full texts of relevant manuscripts were assessed against inclusion criteria. Discrepancies between opinions were solved through discussion or by the third author (L.P.). Only SRs and/or MA of RCTs on interventions for NeuP, as defined by the IASP were included.[12] Excluded from consideration were SRs that were not published in full text in a peer-reviewed journal.

Data Abstraction

From the included SRs, data on efficacy and safety outcomes and outcome measures were extracted in a data abstraction form. The form was first piloted by all team members using 10 random SRs from the sample. Two pairs of authors independently read each article and extracted relevant data (M.J., M.B./M.J., and D.M.). Independent extractions were compared by 1 author (K.V.), and discrepancies resolved by another author (S.D.).

The following data items were extracted: author, publication year, a list of outcomes from the methods and from the results, including both efficacy and safety outcomes, a list of tools and modes for measuring efficacy and safety outcome domains, and primary and secondary outcomes defined in each study. All extracted outcomes were categorized into domains according to the IMMPACT recommendations by 1 author (S.D.).[7]

Comparison With the Recommended Outcome Domains and Outcome Measures

Extracted outcome domains were evaluated against the 6 core domains from a COS for chronic pain that was recommended by the IMMPACT.[7] Supplemental outcome domains according to IMMPACT recommendations were also analyzed.[7] Outcome measures used in the included studies were compared with the IMMPACT 2005 COMs recommended for chronic pain.[8]

Statistics

Descriptive statistics were used to present the frequency of using safety and efficacy outcome domains in the SRs on NeuP, the frequency of using the recommended core outcome domains for NeuP, and temporal changes in using various outcome domains. To analyze outcome domains that were used before and after the publication of the 2003 IMMPACT recommendations, the end of 2004 was set as a cutoff date to account for a possible time delay in the publication of the NeuP manuscripts. Empty reviews (Cochrane reviews that could not find a single study eligible for inclusion) were not used for the comparison of prespecified with reported outcome domains, as they did not have any included studies.

The normality of data distribution was checked using Kolmogorov-Smirnov test. Microsoft Excel (Microsoft Corp., Redmond, WA) and IBM SPSS Statistics for Windows, version 19.0.0 (IBM Corp., Armonk, NY) were used for analyses. Statistical significance was defined at $P < 0.05$.

RESULTS

Literature Search

The literature search yielded 2412 unique bibliographic records, of which 2070 were excluded according to exclusion criteria. After reading 342 full texts, 97 SRs and/or MAs of

NeuP interventions were included (for the references of included SRs, see Table, Supplemental Digital Content 1, http://links.lww.com/CJP/A467). A list of studies excluded after the full-text screening with reasons for exclusion is available upon request.

General Study Characteristics

The 97 included NeuP reviews were published between 1995 and 2015 and included 1429 original RCTs. The most of the SRs studied painful diabetic neuropathy (n = 24) and lumbosacral radiculopathy (n = 15). Various pharmacologic interventions were analyzed in 57 SRs, 15 SRs examined surgical treatments, whereas the remaining 25 SRs investigated multiple interventions. There were 7 SRs that did not contain any RCT (empty reviews).

The SRs reported between 1 and 37, median (interquartile range [IQR]): 9.5 (6 to 17.25), outcome measures in the results, leading to a total of 240 different outcome measures used for the assessment of treatment efficacy and safety across the 90 SRs with included RCTs. Not a single outcome measure was reported in all SRs.

In addition to the 6 core outcome domains, results for 4 supplemental IMMPACT domains (clinician or surrogate ratings of global improvement, role functioning, pharmacoeconomic measures, biological markers), and 1 additional domain that did not fall into IMMPACT classification were found.

The primary outcome was not specified in 28, and secondary in 43 of 97 included NeuP SRs. None of the included SRs stated whether they considered a COS recommended by the IMMPACT for the selection of relevant outcome domains. Only 9 SRs mentioned IMMPACT recommendations for establishing at least some of the outcome measures used. Additional 3 SRs mentioned ACTINPAIN writing group of the IASP Special Interest Group (SIG) on Systematic Reviews in Pain Relief and/or the Cochrane Pain, Palliative and Supportive Care Systematic Review Group recommendations related to outcome selection.

Core Outcome Domains in Empty NeuP Cochrane Reviews

There were 7 NeuP SRs without included RCTs which were therefore presented separately. In the methods section of 6 SRs, the authors specified 3 IMMPACT chronic pain core outcome domains (pain, physical function, and adverse events). One SR, besides above-mentioned domains from the COS, planned to include emotional functioning and participant ratings of improvement and satisfaction with treatment.

Outcome Domains in Methods

The median number of all outcome domains indicated in methods of 90 NeuP SRs was 4 (IQR, 3 to 5; minimum to maximum, 0 to 9). The median number of planned COS domains was 3 (IQR, 2 to 4; minimum to maximum, 0 to 6). Only 3 SRs planned to include all 6 domains from IMMPACT-recommended COS for chronic pain, whereas 5 did not plan to include a single core domain.

Pain was the most common (86%) core outcome domain mentioned in methods, followed by symptoms and adverse events (76%). Emotional functioning was the least specified COS domain. From the IMMPACT supplemental domains, biological markers (eg, sensory testing, nerve conduction studies, change in neurological status) were the most frequent domain (31%). The detailed use of outcome domains in methods of 90 NeuP SRs with included RCTs is presented in Table 1.

The analysis of temporal trends in the adherence to IMMPACT COS (Fig. 1A) showed that none of the SRs published before January 2005 specified emotional functioning in the methods, compared with 14% of SRs published afterward. Physical functioning was specified double (22% vs. 46%), and participant ratings of improvement and treatment satisfaction was specified 4 times more (11% vs. 49%) in the methods of SRs published after January 2005.

Outcome Domains in Results

This section only presents analyses for 90 SRs that included primary studies. The median number of all outcome domains reported in results of those SRs was 5 (IQR, 3 to 6; minimum to maximum, 1 to 9); the median number of domains from the IMMPACT-recommended COS reported in their results was 4 (IQR, 2.75 to 5; minimum to maximum, 1 to 6).

According to the IMMPACT, the majority of NeuP SRs evaluated a combination of 4 (28%) and 3 (21%) of 6 recommended COS domains. All 6 core domains were found in only 9 SRs, and there were no SRs that did not include at least 1 core domain.

Pain was the most commonly assessed COS domain with all except 5 SRs (94%) reporting it in the results, followed by symptoms and adverse events (84%). The most frequently reported supplemental domain, biological markers, and clinician or surrogate ratings of global improvement, were found in at least a third of included SRs (Table 1).

Nine SRs did not report 1 COS domain specified in the methods: data for physical functioning was most commonly missing from the SR results. In contrast, 35 NeuP SRs reported results for more COS domains than specified in the methods, and 5 SRs reported results for ≥ 1 IMMPACT supplemental outcome domains.

A comparison of NeuP SRs published before and after January 2005 showed that none of the 9 SRs published before January 2005 reported outcomes results defined by

TABLE 1. Comparison of Outcome Domains in Methods and Results

Domain	Methods (N [%])	Results (N [%])
IMMPACT Core Outcome Domains		
1. Pain	77 (86)	85 (94)
2. Physical functioning	39 (43)	48 (53)
3. Emotional functioning	11 (12)	26 (29)
4. Participant ratings of improvement and satisfaction with treatment	41 (46)	44 (49)
5. Symptoms and adverse events	68 (76)	76 (84)
6. Participant disposition	36 (40)	45 (50)
IMMPACT Supplemental Outcome Domains		
7. Clinician or surrogate ratings of global improvement	20 (22)	31 (34)
8. Role functioning	15 (17)	17 (19)
9. Pharmacoeconomic measures	0 (0)	6 (7)
10. Biological markers	28 (31)	34 (38)
Other domains		
11. Other outcomes	20 (22)	20 (22)

IMMPACT indicates Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.

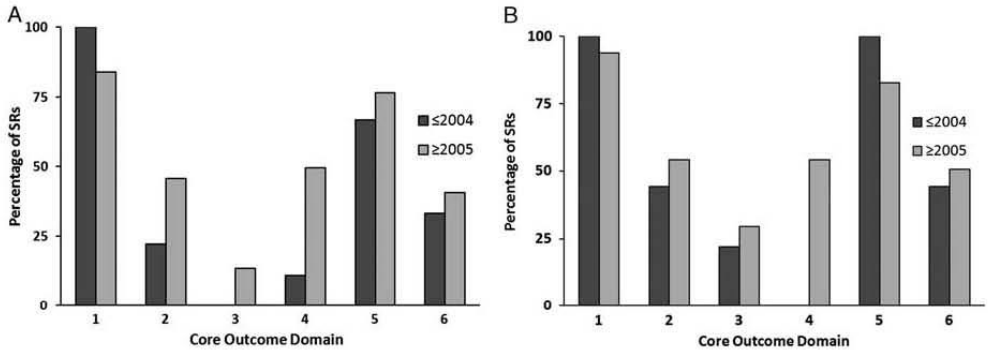

FIGURE 1. Temporal analysis of adherence of individual SRs to Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials–recommended core outcome domains for chronic pain. The bar graph shows the percentage of SRs that included each of the 6 core domains in the methods (A) and results (B) according to publication year (dark gray published before or in 2004 [n = 9], light gray after the year 2004 [n = 81]). Core domains are pain (1), physical functioning (2), emotional functioning (3), participant ratings of global improvement and satisfaction with treatment (4), symptoms and adverse events (5), and participant disposition (6). SRs indicate systematic reviews.

IMMPACT for the core domain participant ratings of improvement and satisfaction with treatment, whereas 44 of 81 SRs published afterward presented those results. The proportions of SRs that adhered to other COS domains were similar (Fig. 1B).

Outcome Measures in Results According to the IMMPACT Core Outcome Domains

Pain

Pain was assessed using 61 different outcome measures (Table 2). Pain intensity was rated on Visual Analog Scales (VASs) (see outcome measures; Supplemental Digital Content 2, http://links.lww.com/CJP/A475) (0 to 10 or 0 to 100) in 59 SRs, 11-point Numerical Rating Scale (NRS) in 29, and Verbal Rating Scales (VRS) in 14 SRs. Mean pain score at endpoint (using various scales) was used in 10 SRs. Other outcome measures of pain intensity reported in <10% of included studies were 4-point categorical scale, the Gracely Pain Scale and its modified version, ordinal scale 1 to 5, the Brief Pain Inventory (BPI) and its Short Form, 7-point thermometer scale, the VITAS scale, and the Short Form-36 Health Survey (SF-36) Bodily Pain section. Pain on movement was assessed in only 2 SRs.

Pain relief was most commonly analyzed as at least 50% reduction (n = 58) or at least 30% reduction in pain from baseline (n = 32) on VAS, NRS, and nonspecified pain scale. Final pain state, defined as "lack of pain or mild pain," was reported in 10 SRs. Other pain measures were used less frequently, with various definitions of improvement.

Pain quality and temporal aspects of pain were assessed using 17 measurement instruments. The McGill Pain Questionnaire (MPQ) was most frequently used measure of pain quality (n = 14), followed by the Short Form MPQ (SF-MPQ, n = 6).

The use of rescue analgesics was most commonly assessed as the dose of all analgesics, nonsteroidal anti-inflammatory drugs, and opioids consumed (n = 24).

Physical Functioning

Overall, 74 different outcome measures were used to evaluate this core domain in 48 NeuP SRs: 55 for physical function (disability), 11 for health-related quality of life, and 8 for sleep interference. Table 3 presents specific outcome measures used and the frequency of their use across included studies. The most common were the SF-36 (n = 18), the Oswestry Disability Index (n = 14), the Roland-Morris disability questionnaire (n = 11), hand grip strength (n = 14), and change in sleep rating scores (n = 9). All other items were represented in <10% of included studies of which, there were 38 outcome measures used in only 1 SR.

Emotional Functioning

Twenty-six NeuP SRs presented 13 different outcome measures used to capture emotional functioning. The Beck Depression Inventory, the Profile of Mood States, the Hospital Anxiety Depression Scale, and the Carpal Tunnel Outcome Assessment—Mental Distress Scale were each used in 3 SRs, and others measures even less frequently (Table 4).

Participant Ratings of Improvement and Satisfaction With Treatment

The 17 outcome measures found for this domain in 44 NeuP SRs are presented in Table 5. The most common were the Patient Global Impression of Change Scale (PGIC) "much or very much improved" used in 11 SRs and "clinically significant improvement" on PGIC (not defined) used in 7 SRs. Three SRs used PGIC "very much improved," and 4 any or slight improvement on PGIC. Other measures were used less frequently (eg, the Global Perceived Effect, the Global Assessment of Therapeutic Effect). Eight outcome measures were used to assess patient satisfaction. The measurement tool or mode was not reported in 9 NeuP SRs, and specified measures were: 4-point and 5-point satisfaction scale, VAS score (0 to 100), "good or very good" patient satisfaction, the relative risk of having fair or poor treatment satisfaction, the Patient Satisfaction Index, and the Patient Satisfaction Scale (0 to 10).

Symptoms and Adverse Events

The incidence (n = 70) and severity (n = 60) were most commonly used to report adverse events, and 13 NeuP studies only mentioned them without discussing the incidence or severity of adverse events. Surgical morbidity

TABLE 2. Outcome Measures for the IMMPACT-recommended Core Domain Pain and a Comparison With the NeuPSIG Recommendations

Outcome Measures	N (%)	IMMPACT	NeuPSIG
Pain intensity		✓	✓
VAS	59 (66)	×	✓
Eleven-point NRS	29 (32)	✓[a]	✓
VRS	14 (16)	✓	✓
Mean pain score at endpoint	10 (11)	/	✓
Four-point categorical scale	6 (6.7)	/	/
Gracely Pain Scale	3 (3.3)	/	✓
Modified Gracely Pain Scale	1 (1.1)	/	/
Ordinal scale 1-5	1 (1.1)	/	/
BPI	1 (1.1)	/	✓
BPI (Short Form)	1 (1.1)	/	/
Seven-point thermometer scale	1 (1.1)	/	/
VITAS scale	1 (1.1)	/	/
Short Form-36 Health Survey (SF-36), Bodily Pain	1 (1.1)	/	/
Not specified	1 (1.1)	/	/
Pain relief		✓	✓
At least 50% pain relief (scale not specified)	21 (23)	/	/
At least 50% pain relief on VAS	16 (18)	✓	/
At least 50% pain relief (substantial) on NRS	11 (12)	✓	✓
At least 50% pain relief on Likert Scale	3 (3.3)	/	/
At least 50% relief on neuropathy symptom score	1 (1.1)	/	/
At least 30% pain relief on VAS	10 (11)	✓	/
At least 30% pain relief on NRS	9 (10)	✓	✓
At least 30% pain relief (scale not specified)	9 (10)	/	/
At least 30% total symptom score reduction	1 (1.1)	/	/
Reduction in baseline pain score (% not specified)	27 (30)	/	/
Final pain state: lack of pain/ mild pain	10 (11)	/	/
At least moderate or good improvement in pain on a categorical scale	8 (8.9)	/	/
Pain relief "excellent" (no pain) or "good" (mild pain) ("complete" or "good" responses on the verbal rating 6-point scale or Patient Global Evaluation of Pain Relief) (complete, a lot, moderate, slight, none, worse).	6 (6.7)	/	/
At least 2-point NRS reduction from baseline	6 (6.7)	/	/
Six-point VRS for pain relief ("complete"(6), "good" (5), "moderate" (4), "slight" (3), "none" (2), or "worse" (1)	5 (5.6)	/	/
Pain much or moderately improved	3 (3.3)	/	/
Six-item categorical scale (modified pain relief scale): 0 = no pain relief, 5 = complete pain relief, % not defined	3 (3.3)	/	/
Change in NRS-3 score from baseline	2 (2.2)	/	/
≥ 10 mm improvement on VAS (minimal)	2 (2.2)	/	/
At least 2-point improvement on VAS (appreciable)	2 (2.2)	/	/
At least 40% relief on VAS	1 (1.1)	/	/
At least 75% pain relief (scale not specified)	1 (1.1)	/	/
At least 2-point improvement on Verbal Pain Scale	1 (1.1)	/	/
Pain relief scale 3 points: complete vs. partial vs. no pain relief	1 (1.1)	/	/
Pain quality and temporal aspects of pain		✓	✓
MPQ	14 (16)	/	×
Short Form MPQ	6 (6.7)	✓	✓
Allodynia severity rating scale	4 (4.4)	/	/
Neuropathic Pain Scale	3 (3.3)	/	✓
Frequency, duration, severity of attacks (Trigeminal neuralgia)	3 (3.3)	✓	/
Six-item neuropathy scale	2 (2.2)	/	✓
Neuropathic total symptom score 6	2 (2.2)	/	✓
Pain: symptom distribution on body chart	2 (2.2)	/	
Time to return of pain	2 (2.2)	✓	/
Ratings of 4 pain aspects (constant, paroxysmal, touch evoked, pressure evoked) on 0-10 scale	2 (2.2)	/	/
Dutch version of MPQ	1 (1.1)	/	/
Neuropathic pain symptom inventory	1 (1.1)	/	✓
West-Haven Yale Multidimensional Pain Inventory	1 (1.1)	/	✓
Trigeminal neuralgia score	1 (1.1)	/	/
Categorical phantom pain intensity (0 = none, 1 = mild pain, 2 = moderate pain, 3 = severe pain)	1 (1.1)	/	/
Time required for relief of pain (≤ 50% original VAS)	1 (1.1)	✓	/
Onset of therapeutic effect	1 (1.1)	/	/
Rescue analgesics and concomitant pain treatments		✓	×
Analgesic consumption dose	18 (20)	✓	/
NSAIDs consumption	4 (4.4)	/	/
Opioid consumption	2 (2.2)	/	/
Decrease in number of used tablets/day	1 (1.1)	/	/
Proportion of days rescue medication administered	1 (1.1)	/	/
Type, frequency and change of medication	1 (1.1)	/	/

✓Recommended outcome measure.
✓[a] IMMPACT core outcome measure.
×Not recommended.
/Not mentioned or not applicable.
BPI indicates Brief Pain Inventory; IMMPACT, Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; MPQ, McGill Pain questionnaire; NeuPSIG, Neuropathic Pain Special Interest Group of the International Association for the Study of Pain; NRS, Numerical Rating Scale, NSAIDs, Nonsteroidal anti-inflammatory drugs; SF-36, Short Form-36 Health Survey; VAS, Visual Analog Scale.

(eg, blood loss, incidental durotomies, nerve root injuries, surgical site infections) was presented in 9 NeuP SRs. Only 1 SR used a 27-item checklist for the capture of adverse events.

Participant Disposition

This domain was presented in 45 NeuP SRs. Premature participant withdrawal from the trial due to adverse events (n = 38) was most commonly reported, followed by withdrawals due to lack of efficacy (n = 18) and all-cause withdrawals (n = 18).

TABLE 3. Outcome Measures for the IMMPACT-recommended Core Domain Physical Functioning and a Comparison With the NeuPSIG Recommendations

Outcome Measures	N (%)	IMMPACT	NeuPSIG
Health-related quality of life		✓	✓
SF-36 (all dimensions)	18 (20)	✓	✓
EQ-5D	6 (6.7)	/	✓
SF-12	4 (4.4)	/	/
Nottingham Health Profile	4 (4.4)	/	/
100 mm VAS QoL	2 (2.2)	/	/
Sickness Impact Profile	1 (1.1)	/	/
Patients' lifestyle (Grogono and Woodgate[13])	1 (1.1)	/	/
Norfolk QoL-DN	1 (1.1)	/	/
Twelve-item General Health Questionnaire	1 (1.1)	/	/
Twenty eight-item Taiwanese version of the WHO-QOL-BREF questionnaire	1 (1.1)	/	/
Not specified	1 (1.1)	/	/
Physical function/disability		✓	✓
Oswestry Disability Index	14 (16)	/	✓
Roland-Morris disability questionnaire	11 (12)	✓	/
Grip strength (kg)	9 (10)	/	/
Pinch strength (kg)	8 (8.9)	/	/
SF-36: physical functioning	8 (8.9)	/	/
Function Status Scale of the Boston Carpal Tunnel Syndrome Questionnaire	7 (7.8)	/	/
Recovery of the ability to perform activities of daily living	6 (6.7)	/	/
North American Spine Society questionnaire	3 (3.3)	/	/
Straight leg raising test	3 (3.3)	/	/
Finger floor distance (cm)	3 (3.3)	/	/
The Schober Index (cm) Lumbar flexion	3 (3.3)	/	/
Hand-Finger Functioning (HAND) scale	3 (3.3)	/	/
Carpal Tunnel Outcome Assessment Physical Distress	3 (3.3)	/	/
Return of hand use/hand function	3 (3.3)	/	/
Wrist motion (flexion/extension)	3 (3.3)	/	/
Upper limb tension test	2 (2.2)	/	/
Jebson score	2 (2.2)	/	/
Brief Pain Inventory physical functioning score	2 (2.2)	✓[a]	✓
West Haven-Yale Multidimensional Pain Inventory Subscale pain interference	2 (2.2)	✓[a]	/
EIFEL (French version of Roland-Morris disability questionnaire)	2 (2.2)	/	/
Hannover functional ability	2 (2.2)	/	/
Pain Disability Index	2 (2.2)	/	✓
Dallas Pain Questionnaire	2 (2.2)	/	✓
Prolo scale	2 (2.2)	/	/
Mobility of the lumbar spine	2 (2.2)	/	/
Disability of the arm shoulder questionnaire	2 (2.2)	/	/
Disability rated by the investigator (none, mild, moderate, and severe disability)	1 (1.1)	/	/
SF-36 Body Pain Scale—function	1 (1.1)	/	/
SF-12: physical functioning	1 (1.1)	/	/
Japanese Orthopedic Association score	1 (1.1)	/	/
Functional Independence Measure	1 (1.1)	/	/
Craig Handicap Assessment and Reporting Technique	1 (1.1)	/	/
Barthel Index function	1 (1.1)	/	/
Backill Scale	1 (1.1)	/	/
Prolo Scale—functional score, SPINE	1 (1.1)	/	/
Neurological impairment score	1 (1.1)	/	/
Neurological impairment score—lower limb	1 (1.1)	/	/
Lumbar disease grade	1 (1.1)	/	/
Spinal stiffness (0-4)	1 (1.1)	/	/
Four self-selected items on 4-point scale	1 (1.1)	/	/
Lattinen test (LQ) disability (spinal cord injury)	1 (1.1)	/	/
Change in walking distance	1 (1.1)	/	/
Hand function ordinal questionnaire (13-items modified from Levine/Pransky, scored on ordinal scale 1-5)	1 (1.1)	/	/
Moberg Pick-up Test (carpal tunnel)	1 (1.1)	/	/
Function using the Grooved Pegboard test	1 (1.1)	/	/
Canadian Occupational Performance Measure	1 (1.1)	/	/
Neck Disability Index	1 (1.1)	/	/
Cervical range of motion	1 (1.1)	/	/
Cervical muscle strength, not specified	1 (1.1)	/	/
McMaster-Toronto Arthritis Patient Function Preference Questionnaire	1 (1.1)	/	/
Decrease in perceived handicap (VAS mm)	1 (1.1)	/	/
Disability: subjective estimation of disability: % improved	1 (1.1)	/	/
Self-reported functional status-mean change from baseline	1 (1.1)	/	/
Not specified	2 (2.2)	/	/
Sleep		✓	✓
Change in sleep rating scores (scales not specified)	9 (10)	/	/
Sleep (linear or categorical scales)	2 (2.2)	/	/
Sleep in hours	2 (2.2)	/	/
No. of nights that the patient woke due to the symptoms in a week	2 (2.2)	/	/
Sleep Interference Scale	1 (1.1)	/	✓
Sleep NRS 0-10 scale	1 (1.1)	/	/
Lattinen test (LQ)—sleep quality (spinal cord injury)	1 (1.1)	/	/
Sleep disturbance change on NRS (0-10)	1 (1.1)	/	/

(*Continued*)

TABLE 3. (*continued*)

✓Recommended outcome measure.
✓[a] IMMPACT core outcome measure.
/Not mentioned or not applicable.
EQ-5D indicates EuroQol 5 dimensions questionnaire; IMMPACT Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; NeuPSIG, Neuropathic Pain Special Interest Group of the International Association for the Study of Pain; Norfolk QoL-DN, Quality of Life for Diabetic Neuropathy questionnaire; NRS, Numerical Rating Scale; QoL, quality of life; SF-36, Short Form-36 Health Survey; SF-12, 12-Item Short Form Health Survey; VAS, Visual Analog Scale; VRS, Verbal Rating Scale; WHO-QOL-BREF, World Health Organization QOL-BREF questionnaire.

Outcome Measures According to the IMMPACT Supplemental Outcome Domains

Clinician or surrogate ratings of global improvement were found in approximately one-third of NeuP SRs (Table 6).

TABLE 4. Outcome Measures for the IMMPACT-recommended Core Domain Emotional Functioning and a Comparison With the NeuPSIG Recommendations

Outcome Measures	N (%)	IMMPACT	NeuPSIG
Beck Depression Inventory	3 (3.3)	✓[a]	✓
Profile of Mood States	3 (3.3)	✓[a]	✓
Hospital Anxiety Depression Scale	3 (3.3)	/	✓
Carpal Tunnel Outcome Assessment Mental Distress Scale	3 (3.3)	/	/
SF-36: role emotional	2 (2.2)	/	/
State-Trait Anxiety Inventory	2 (2.2)	/	/
Center for Epidemiologic Studies Depression Scale Short Form (CESD-SF)	2 (2.2)	/	/
SF-MPQ affective score	1 (1.1)	/	/
Fear avoidance beliefs questionnaire	1 (1.1)	/	/
Center Epidemiologic Depression Scale	1 (1.1)	/	/
Brief Stress Scale	1 (1.1)	/	/
Satisfaction With Life Scale	1 (1.1)	/	/
Han Hamilton Anxiety Scale score	1 (1.1)	/	/

✓Recommended outcome measure.
✓[a] IMMPACT core outcome measure.
/Not mentioned or not applicable.
IMMPACT indicates the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; NeuPSIG Neuropathic Pain Special Interest Group of the International Association for the Study of Pain; SF-MPQ, Short Form McGill Pain Questionnaire; SF-36, Short Form-36 Health Survey.

The Clinician Global Impression of Change Scale was most commonly used (n = 11), with different definitions of improvement. Patient preference was measured in 5 SR, although the measurement tool was not defined.

Nineteen NeuP SRs assessed outcome measures for supplemental domain role functioning. All except 1 SR assessed work status. Measures most commonly used were the rate (n = 8) or time to return to work (n = 6), and duration of sick leave (n = 3). Other measures were used each in only 1 SRs (3-point scale, the VAS scale, the number of hours of employment, and percentage improvement in interfering or stopping with work). Social dysfunction was measured in 1 SRs as a change on the NRS scale (0 to 10).

The cost of treatment was the only pharmacoeconomic measure analyzed. Six NeuP SRs assessed costs: the Prolo scale—Economic score was used in 2 SRs, whereas other did not define how they assessed this outcome.

Supplemental assessment domain biological markers were frequently used (n = 38). There were 21 different measures identified for capturing outcomes such as neurological symptom improvement used in 22 NeuP SRs, electrophysiological parameters (eg, nerve conduction velocities, distal sensory and motor latencies) used in 20 SRs, and clinical neurological status (eg, vibration perception threshold, sensitivity to monofilaments, 2-point discrimination test) used in 18 SRs. Other outcome measures, used less frequently, are presented in Table 7.

Other Outcome Measures Domain

There were 5 outcome measures reported in 20 SRs that did not fall into the IMMPACT core or supplemental domains:

TABLE 5. Outcome Measures for the IMMPACT-recommended Core Domain Participant Ratings of Global Improvement and Satisfaction With Treatment and a Comparison With the NeuPSIG Recommendations

Outcome Measures	N (%)	IMMPACT	NeuPSIG
PGIC		✓[a]	✓
PGIC "much or very much improved"	11 (12)	/	/
PGIC "clinically significant improvement" (% not specified)	7 (7.8)	/	/
PGIC "very much improved"	3 (3.3)	/	/
PGIC "improved slightly"	2 (2.2)	/	/
PGIC any improvement	2 (2.2)	/	/
Satisfaction, not specified	9 (10)	/	/
Satisfaction 4-point scale (completely satisfied, very satisfied, rather satisfied, or dissatisfied) or (excellent, good, fair, poor)	6 (6.7)	/	/
MacNab criteria (excellent, good, fair, poor) spine	4 (4.4)	/	/
Satisfaction 5-point scale (completely satisfied," "almost satisfied," "moderately satisfied," "somewhat satisfied," and "dissatisfied")	3 (3.3)	/	/
Patient-reported global assessment of treatment "very good" or "excellent"	2 (2.2)	/	/
Satisfaction VAS score (0-100)	2 (2.2)	/	/
Good or very good Patient satisfaction	2 (2.2)	/	/
RR of having fair or poor treatment satisfaction	2 (2.2)	/	/
Patient's global assessment of therapeutic effect	1 (1.1)	/	/
Global perceived effect: Global Rating of Change Scale improvement	1 (1.1)	/	/
Patient Satisfaction Index	1 (1.1)	/	/
Patient Satisfaction Scale: "0" very dissatisfied to "10" very satisfied	1 (1.1)	/	/

✓Recommended outcome measure.
✓[a] IMMPACT core outcome measure.
/Not mentioned or not applicable.
IMMPACT indicates Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; NeuPSIG, Neuropathic Pain Special Interest Group of the International Association for the Study of Pain; PGIC, Patient Global Impression of Change Scale; RR, risk ratio; VAS, Visual Analog Scale.

reoperation rate (n = 11), need for surgery as efficacy measure for conservative treatments (n = 9), recurrence rate (n = 5), procedure duration (n = 7), and length of hospital stay (n = 4).

DISCUSSION

This study found that authors of SRs and/or MAs of RCTs of interventions for NeuP insufficiently adhere to the COS recommended by the IMMPACT initiative for the evaluation of treatment efficacy and safety in chronic pain trials. Overall, the included SRs reported a median 4 of 6 IMMPACT core domains and a median 5 of 11 identified domains. Only 10% of the SRs presented outcomes for all 6 IMMPACT core outcome domains, whereas a quarter

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TABLE 6. Outcome Measures for the IMMPACT-recommended Supplemental Domain Clinician or Surrogate Ratings of Global Improvement

Outcome Measures	N (%)
CGIC clinically significant improvement, % not specified	5 (5.6)
CGIC any improvement	5 (5.6)
CGIC much or very much or moderately improved	1 (1.1)
Notable improvement in global assessment	4 (4.4)
Clinicians perception of recovery (working capacity, neurological deficits, pain, and mobility of the spine; relapse)	3 (3.3)
Various categorical scales for improvement	3 (3.3)
Number of responders, not specified	3 (3.3)
Seven-point global rating scale, % not specified	2 (2.2)
Overall improvement (No. participants with good to excellent improvement)	2 (2.2)
Overall improvement (completely normal hands based on electroneuromyography)	2 (2.2)
Treatment efficacy 3-point scale, % not specified	2 (2.2)
TCM syndrome score criteria of diabetic peripheral neuropathy reduction of 30% or more	2 (2.2)
Global measure of improvement	1 (1.1)
Global symptom improvement, 3 scale markedly effective,' "effective," "ineffective"	1 (1.1)
Global effect (cured rate complete relief of symptoms) on a 4-point scale (cured, outstandingly effective, effective/improved, and ineffective)	1 (1.1)
Improvement in symptoms at least 50% on a global symptom score (GSS)	1 (1.1)
Treatment efficacy 4-point scale, % not specified (no efficacy, slight, moderate, good, or very good)	1 (1.1)
Treatment efficacy 5-point scale, % not specified	1 (1.1)
Percentage of the wrists achieving 20%/50%/70% response in nocturnal paresthesias as VAS score; pain, and functional impairment	1 (1.1)
Not specified	4 (4.4)

CGIC indicates Clinical Global Impression of Change; IMMPACT, Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; TCM, Traditional Chinese medicine; VAS, Visual Analog Scale.

TABLE 7. Outcome Measures for the IMMPACT-recommended Supplemental Domain Biological Markers

Outcome Measures	N (%)
Neurological symptoms improvement (such as paresthesia, numbness)	22 (24)
Nerve conduction studies and other electrophysiological measures	20 (22)
Neurological status (vibration perception threshold, sensitivity to monofilament, 2-point discrimination…)	18 (20)
Symptom Severity Scale on Boston Carpal Tunnel Syndrome Questionnaire (rates 11 items on ordinal scale 1: no symptom, to 5: the most severe symptom) (Levine)	7 (7.8)
Nocturnal symptoms (carpal tunnel)	6 (6.7)
McGowan score ulnar tunnel clinical score	2 (2.2)
Louisiana State University Medical Center score ulnar tunnel clinical score	2 (2.2)
Bishop score ulnar tunnel clinical score	2 (2.2)
Medical Research Council (MRC) clinical score ulnar tunnel	2 (2.2)
Global symptom score 0-10 Carpal tunnel	2 (2.2)
Overall severity score 1-6 Carpal tunnel	2 (2.2)
Sciatica Bothersomeness Index	2 (2.2)
Skin microvascular blood flow	1 (1.1)
Hand volume carpal tunnel	1 (1.1)
Yale Sensory Scale	1 (1.1)
Phalen test time (time from which the wrist is bent to the onset of symptoms)	1 (1.1)
Symptom total point carpal tunnel-sum of 5 scores (symptomatic = 1 , asymptomatic = 0 points) for 5 symptoms (hand pain, tingling, numbness, nocturnal numbness, and interrupted sleep)	1 (1.1)
Phasic spasticity: NRS (0-4)	1 (1.1)
Sciatica Frequency Index	1 (1.1)
Autonomic symptoms (oral dryness, dysuria)	1 (1.1)
Development of foot ulcers	1 (1.1)

IMMPACT indicates Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; NRS, Numerical Rating Scale.

evaluated outcomes for only 1 or 2 core domains. This finding indicates that in SRs on NeuP, there is insufficient compliance with the COS of domains proposed by the IMMPACT.

The results of this study showed that pain was the most commonly reported IMMPACT core outcome domain, which is in agreement with another study that analyzed the use of outcome measures in NeuP.[9] They reported that physical functioning was used in only 15% of included SRs, which is much lower than our results indicate (53%). In addition, in their study the core domain symptoms and adverse events were not reported, which was the second most commonly assessed domain in this study.

SRs that captured the core domain pain most commonly used VAS and NRS scales, with the VRS being the third most commonly used tool for the assessment of pain intensity. Although VAS or NRS scales (with VRS scales used as a secondary outcome) are recommended by the NeuPSIG[14] for pain intensity measurement, the IMMPACT initiative does not recommend the use of VAS scales. The IMMPACT identified 11-point NRS scale as a COM, except in conditions for which reliable and valid measures that do not use an NRS are routinely used or in circumstances in which numerical ratings may be problematic, when VRS scales are recommended.[8]

Pain relief was mostly assessed as at least 30% or 50% reduction in pain intensity from baseline, with pain relief scales less frequently used. This finding is in accordance with the IMMPACT COMs[8] and NeuPSIG recommendations[14] for the measurement of treatment response.

The most frequently reported measures of the sensory and affective dimensions of pain were the MPQ and its Short Form (SF-MPQ). Although the SF-MPQ is validated in chronic pain trials and recommended by the IMMPACT as a secondary outcome measure,[8] it has not been validated for NeuP, and its sensitivity requires further confirmation.[14] The validated NeuP quality measures recommended by the NeuPSIG for the evaluation of treatment effects on neuropathic symptoms (the Neuropathic Pain Scale, the Neuropathic pain symptom inventory, the Neuropathic total symptom score 6) were used in <10% of SRs.

This study revealed that the use of rescue medication was reported in one-fifth of SRs. Although recommended as a COM in chronic pain trials by the IMMPACT,[8] the NeuPSIG presented conflicting evidence for the usefulness of this outcome in the setting of NeuP, explaining the discrepancy with the poor treatment response of NeuP to conventional analgesics.[14]

Emotional functioning was the least frequently captured domain. Moreover, NeuP SRs mostly focused on the assessment of mood and anxiety: only 1 SR assessed the fear

of movement, and none passive coping and catastrophizing, which are measures recommended by the NeuPSIG. The IMMPACT recommended the Beck Depression Inventory and the Profile of Mood States as COMs of emotional functioning, both rarely used in included SRs.

Both IMMPACT and NeuPSIG recommended the use of disease-specific measures of the interference of pain with physical functioning (the West Haven-Yale Multidimensional Pain Inventory [MPI] Interference Scale or the BPI pain interference items), which were used in only 4 SRs. The most commonly used disability scales were the Oswestry Disability Index and the Roland-Morris Questionnaire, showed as equally responsive in patients with radicular leg pain.[14] Condition-specific and general disability questionnaires have been used for the assessment of health-related quality of life. With the caveat that there is no generic HRQoL instrument sufficiently validated for use in NeuP, NeuPSIG[14] has recommended using Medical Outcomes Survey Short Form, SF-36, which is also recommended by IMMPACT.[8] The SF-36 was most commonly used HRQoL measure in this study, what is in agreement with both recommendations.

The Global Impression of Change measured by the patient (PGIC), an instrument used for the evaluation of global treatment effect, is recommended by both IMMPACT (as a COM)[8] and NeuPSIG.[14] Findings of this study show that 25 NeuP SRs assessed this outcome using various definitions of improvement. Some additional outcome measures of global assessment, such as patient satisfaction or treatment preference, were also found. The NeuPSIG also recommends using the Clinician Global Impression of Change Scale, and it is considered a supplementary outcome domain by IMMPACT.[7]

Two important core outcome domains within IMMPACT-recommended outcome measures (not found in NeuPSIG recommendations) are adverse events and participant disposition, reported in 84% and 50% of SRs with included studies, respectively. The low reporting rate of adherence to investigated treatments and reasons for premature withdrawal could be related to insufficient reporting in NeuP RCTs, although this study did not determine whether the SRs authors investigated that. In addition, the reporting rate has not changed since the publication of the IMMPACT core outcome domain recommendations.

In the main analysis of 90 SRs in NeuP that had included trials, 240 different outcome measures used for the assessment of treatment efficacy and safety were found. This finding indicates substantial heterogeneity in the measurement tools used to evaluate the investigated treatments, and limits the comparability of results of those studies. The standardized use of specific treatment outcome measures may improve comparability and clinical applicability of chronic pain management trials.[8]

Many outcome measures included in the NeuP SRs were not recommended by the IMMPACT initiative. Those were most commonly used for capturing outcomes such as neurological symptom improvement, electrophysiological parameters, and clinical neurological status, as well as various disease-specific functional assessment questionnaires; all used in SRs that assessed specific NeuP conditions such as diabetic NeuP, trigeminal neuralgia, compressive neuropathies, and lumbar radicular pain. The IMMPACT initiative emphasized that the recommended outcome measures were expected to be supplemented by any outcome measure relevant for treatment evaluation of specific diseases.[8]

The core outcomes reporting in clinical trials is considered a minimum requirement,[2] not a restriction, and researchers should continue to collect and report other outcomes relevant to the specific research area in addition to COS.[15,16] Furthermore, IMMPACT also recommended supplemental outcome domains that could be considered for inclusion in chronic pain clinical trials, depending on the specific research question.[7] The most commonly presented supplemental domains in NeuP were biological markers and clinician or surrogate ratings of global improvement. None of the studies included interpersonal functioning, coping, neuropsychological assessments of cognitive and motor function or suffering, and other end-of-life issues.

Deficiencies in reporting primary and secondary outcomes in the methods of included studies were also identified. Specifically, the primary outcome was not specified in 28, and secondary in 43 of 97 included SRs.

A comparison of the planned outcome domains with those reported in the results did not reveal many reporting deficiencies. The 2 core domains most frequently specified in the methods and reported in the results of SRs were pain and symptoms and adverse events. Emotional functioning was the least specified, as well as the least presented of 6 core domains. Although 9 SRs did not report 1 core domain defined in the methods, 35 SRs reported results for more core outcome domains than specified.

A temporal analysis of adherence to core domains showed that SRs published after the IMMPACT core domain recommendations[7] increasingly presented results for the participant ratings of improvement and satisfaction with treatment, whereas that domain was not used before the IMMPACT recommendations were published.

SRs of RCTs, with or without a MA, are crucial for evidence-based medicine and evidence-based decision-making.[17] Well-conducted RCTs and SRs allow decision-makers reliable evidence that the outcome of interest is causally associated with the studied intervention. For the production of SRs, it is crucial to have RCTs with sufficiently homogeneous outcomes so that the RCT results can be combined in a MA. If this is not the case, and if the RCT authors use heterogeneous outcomes than the primary studies are not comparable, and it is difficult to combine their results. COS are very important in this respect. The authors do not need to use the recommended COS for certain condition exclusively; they can use additional relevant outcome domains as well, but still, adherence to the recommended COS should be a priority.[2]

In some areas, such as the field of rheumatology, the concept of COS has been present for a while.[3] Despite this fact, the results of a recent analysis that compared outcome domains used in 100 studies (including cohort studies, RCTs, and registry studies) evaluating participants undergoing knee arthroplasty for osteoarthritis against the COS recommended by the OMERACT indicated substantial heterogeneity in that field. The authors concluded that this reduces the usefulness of research evidence and benefits that patients may yield based on the available evidence base.[18]

The situation in the research field with no COS was illustrated recently in a study of Beuscart et al,[19] who analyzed outcomes in RCTs of medication review in older patients; in 47 RCTs they found as many as 327 distinct outcomes, indicating a need for standardized COS.

Some studies cite COS; however, this does not necessarily confirm its use. Barnes and colleagues recently reported results of their study in which they explored

whether citing COS can be a viable approach for measuring uptake of the COS. They assessed whether a number of citations that a report about COS received can be used as a surrogate measure of adherence with the COS. They analyzed 173 manuscripts that were published in 2009 and earlier and found that trials that use relevant COS made only a small proportion of the total number of COS citations. Although trials may have cited COS, it has been used for different reasons such as supporting a definition of a clinical condition, or for information relating to trial designs that were in the COS report.[20]

Much has been written recently about research waste. If clinical trials and SRs do not use COS, then they are hampering comparability and usability of the evidence thus contributing to research waste. Therefore, all efforts that will increase uptake of relevant COS should be supported.[10]

Although specific recommendations for COS reporting were developed for clinical trials, they should be used by systematic reviewers as well.[16] The use of COS in SRs is reported to be rare.[15] It has been reported that even Cochrane SRs, which use more rigorous methodology than other SRs,[21,22] do not use COS as a guide for selections of their outcomes. A survey from 2015 that examined the use of COS and outcome reporting in Cochrane reviews found that none of the 375 analyzed reviews explicitly stated the use of a COS in defining outcomes of interest, although they might have considered a COS without clearly mentioning it.[23] The findings of this study confirm this. Not a single SRs that mentioned a consideration for core outcome domains (COS) recommended by IMMPACT for the selection of relevant outcomes was identified. However, there were 9 SRs that mention that they followed at least one of the recommended IMMPACT outcome measures, and 3 were guided by ACTINPAIN and/or the Cochrane Pain, Palliative, and Supportive Care Group.

Limitations

Although performed consistently, the attempt to group outcomes into distinct domains is not straightforward because some outcome measures are overlapping.

A comparison of the outcomes specified in the methods section of included SRs with the outcomes reported in the results is not ideal, and is considered a limitation of this study. Outcomes prespecified in the published protocols should be sought to allow for the exact comparison, but that was not performed considering that only a minor proportion of SRs had issued a defined protocol before conducting a SR. It is mandatory for Cochrane reviews' authors to publish the review protocol in the Cochrane Database of Systematic Reviews, and since 2011 it is also possible for other SRs' authors to publish their protocols in the PROSPERO registry.[24]

Finally, it should be pointed out that IMMPACT recommendations are not mandatory as it is possible that some of the recommended core domains are not relevant for the specific trial. In that case, IMMPACT group advised reporting the reasons for exclusion of a specific core domain. An analysis of the grounds for exclusion of core outcomes or the reasons for not reporting all outcomes specified in the methods section was not performed in this study. It is possible that desired outcomes could not have been extracted or were not even reported in the studies included in SRs.

CONCLUSIONS

Authors of SRs in the field of NeuP insufficiently use relevant recommended core outcome domains. This should be changed in the future, and more effort needs to be put into the implementation of COS for chronic pain to ensure that the study results can be compared, contrasted, and combined. Although IMMPACT COS for chronic pain is relevant for NeuP trials and SRs, there is a need for defining relevant COS for NeuP as a whole, as well as for different types of pain that fall under the "umbrella term" of NeuP.

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Comparison of methodological quality rating of systematic reviews on neuropathic pain using AMSTAR and R-AMSTAR

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Abstract

Background: Systematic reviews (SRs) in the field of neuropathic pain (NeuP) are increasingly important for decision-making. However, methodological flaws in SRs can reduce the validity of conclusions. Hence, it is important to assess the methodological quality of NeuP SRs critically. Additionally, it remains unclear which assessment tool should be used. We studied the methodological quality of SRs published in the field of NeuP and compared two assessment tools.

Methods: We systematically searched 5 electronic databases to identify SRs of randomized controlled trials of interventions for NeuP available up to March 2015. Two independent reviewers assessed the methodological quality of the studies using the Assessment of Multiple Systematic Reviews (AMSTAR) and the revised AMSTAR (R-AMSTAR) tools. The scores were converted to percentiles and ranked into 4 grades to allow comparison between the two checklists. Gwet's AC1 coefficient was used for interrater reliability assessment.

Results: The 97 included SRs had a wide range of methodological quality scores (AMSTAR median (IQR): 6 (5–8) vs. R-AMSTAR median (IQR): 30 (26–35)). The overall agreement score between the 2 raters was 0.62 (95% CI 0.39–0.86) for AMSTAR and 0.62 (95% CI 0.53–0.70) for R-AMSTAR. The 31 Cochrane systematic reviews (CSRs) were consistently ranked higher than the 66 non-Cochrane systematic reviews (NCSRs). The analysis of individual domains showed the best compliance in a comprehensive literature search (item 3) on both checklists. The results for the domain that was the least compliant differed: conflict of interest (item 11) was the item most poorly reported on AMSTAR vs. publication bias assessment (item 10) on R-AMSTAR. A high positive correlation between the total AMSTAR and R-AMSTAR scores for all SRs, as well as for CSRs and NCSRs, was observed.

Conclusions: The methodological quality of analyzed SRs in the field of NeuP was not optimal, and CSRs had a higher quality than NCSRs. Both AMSTAR and R-AMSTAR tools produced comparable quality ratings. Our results point out to weaknesses in the methodology of existing SRs on interventions for the management NeuP and call for future improvement by better adherence to analyzed quality checklists, either AMSTAR or R-AMSTAR.

Keywords: Neuropathic pain, Systematic review, Methodological quality, AMSTAR, R-AMSTAR, Interrater reliability

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Background

Systematic reviews (SRs) are considered to be of the highest quality in the hierarchy of evidence and are increasingly used for evidence-based decision making [1]. SRs should summarize the literature on a given topic using rigorous methodology. One of the standard features of SR methodology is the assessment of the quality of included primary studies, by using various tools [2].

However, there are also tools for assessing the methodological quality of SRs themselves, such as the Assessment of Multiple Systematic Reviews (AMSTAR), developed in 2007 [3]. AMSTAR was found to be a reliable and valid measurement tool for assessing the methodological quality of SRs [4]. A different group of authors suggested the use of revised AMSTAR (R-AMSTAR) in 2010 [5]. Despite the existence of R-AMSTAR, it was reported that AMSTAR had been used more frequently for the assessment of methodological quality of SRs [6]. This could be because AMSTAR, despite its flaws and many suggestions for its improvement, is shorter and simpler to use [7].

These tools for the assessment of methodological quality of SRs show that many SRs are inadequate. A comprehensive report on 300 SRs published in 2007 showed that their quality of reporting was inconsistent, indicating that readers should not think of SRs as synonymous with high-quality evidence [8]. An updated version of this study, published in 2016, indicated that the number of SRs being published is increasing, but the majority of them are still poorly conducted and reported [9].

Neuropathic pain (NeuP) has been estimated to affect 5–10% of the general population [10–12] and is associated with poor general health and quality of life [13–15]. This research area has received considerable attention from the International Association for the Study of Pain (IASP) as, despite the availability of many drugs and guidelines, NeuP remains under- or untreated in many cases [16]. Several evidence-based guidelines for the management of NeuP have been published in recent years [17–22]. It is of particular importance to ensure that those recommendations are based on high-quality research. It is also important to find out which measurement tool can be recommended for methodological quality rating in this cohort of interventional SRs.

Therefore, our primary aim was to analyze the methodological quality of SRs in the field of NeuP and to compare two different tools for quality assessment because it is still unclear which one is more appropriate. For this purpose, we used AMSTAR, a validated tool, and R-AMSTAR, which still cannot be put at the same level as AMSTAR with respect to validation. Our secondary aims were to calculate the interrater reliability and scoring discrepancies between the two authors and to analyze the overall agreement score between AMSTAR and R-AMSTAR. By assessing the methodological quality of available evidence, we hope to call attention to the current weaknesses of those tools and inspire future researchers to set higher standards in conducting SRs.

Methods

Protocol registration

We developed a protocol for this study a priori and registered it in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42015025832).

Inclusion criteria

We included SRs of randomized controlled trials (RCTs) evaluating efficacy and safety of any therapeutic intervention for NeuP according to the IASP definition [23]. Any comparator and any outcome measure were eligible for inclusion. Studies in any language were eligible.

Exclusion criteria

We excluded individual patient data SRs, SRs that were not interventional (e.g., prognostic, diagnostic accuracy), SRs that included other types of studies besides RCTs, as well as SRs that included a population with disorders that do not satisfy the current IASP criteria for NeuP [23]. We also excluded SRs published only as abstracts.

Study selection

We searched MEDLINE, Cochrane Database of Systematic Reviews, DARE, CINAHL and PsycINFO from the earliest date that each database allowed up to March 9, 2015, without language or publication date restriction. A comprehensive search strategy for MEDLINE (Additional file 1) was developed by combining medical subject heading (MeSH) terms and text words for NeuP conditions with text words for SR/meta-analysis. The MEDLINE strategy was adapted for other databases. Two authors (SD, AJK) independently screened the search results for inclusion using pre-defined relevance criteria at all levels of screening (e.g., title and abstract, full-text review of potentially relevant articles). Discrepancies were resolved by discussion and the involvement of a third author (LP).

Assessment of methodological quality

AMSTAR [24] and R-AMSTAR [5] were applied to all included SRs. We used a newer version of AMSTAR, with explanations available on the tool's website [24]. Before quality assessment, the items on both scales were discussed, and a calibration exercise was performed on one of the included SRs. Summary scores for AMSTAR (possible range 0–11) and R-AMSTAR (possible range 11–44) were calculated by two independent junior research fellows (one clinician and one methodologist) experienced in methodological studies, but without formal experience with these tools (NM, KV). Raters without formal training in

applying AMSTAR and R-AMSTAR were chosen because we did not want previous experience and potentially differing approaches to using AMSTAR and R-AMSTAR (due to ambivalence and multi-layer aspects of some domains) to influence the raters. In this way, the level of expertise of raters was removed as a potential confounding variable in rating the evidence. The AMSTAR tool was applied first to the whole set of included SRs. After approximately 4–6 weeks, the methodological quality rating was repeated with the R-AMSTAR tool. Discrepancies were resolved by the involvement of a third author (SD).

The performance of studies on each AMSTAR domain was rated by looking into the proportion of studies with a score "yes" compared to other possible scores, while the performance on each R-AMSTAR domain was assessed by looking into the percentage of studies with highest scores (scores 4 and 3), with 4 as the maximum score for a domain in R-AMSTAR. A subgroup analysis was made for the differences in methodological quality between Cochrane SRs (CSRs) and non-Cochrane SRs (NCSRs).

Comparison of AMSTAR and R-AMSTAR

The AMSTAR and R-AMSTAR scores of each SR were subsequently converted to percentiles for each checklist to allow for the comparison of quality scores between the different assessment tools. We calculated percentiles by first ranking quality scores from lowest to highest and then taking the value from the ordered list that corresponds to that rank. The percentiles were assigned surrogate grades, as follows: grade A: ≥90%ile, grade B: 80–89%ile, grade C: 70–79%ile, grade D: ≤69%ile, as described previously [5]. Based on the resulting percentile scores, surrogate grades were assigned to each SR. Both total scores and surrogate grades were compared between the two assessment tools.

Interrater agreement

We analyzed the interrater agreement by using Gwet's AC1 coefficient [25]. An overall agreement score, as well as a score for each item, was calculated. We also calculated Cohen's Kappa values and presented the results in Additional file 2 (AMSTAR) and Additional file 3 (R-AMSTAR). Values were calculated for AMSTAR by dichotomizing the responses into the categories "yes" (1 point) versus any other score ("no", "can't answer", "not applicable"; each 0 points). For R-AMSTAR we calculated the interrater agreement on all the criteria in each of the 11 questions, resulting in a total of 41 assessments. The possible responses were "yes" or "no". A study used for calibration exercise was excluded from the calculation [26].

For simplification, we interpreted both interrater agreement measures, Gwet's AC1 coefficient and Cohen's Kappa, as follows: coefficients of less than 0 signify poor agreement; 0.01–0.20 slight agreement; 0.21–0.40 fair agreement; 0.41–0.60 moderate agreement; 0.61–0.80 substantial agreement; and 0.81–0.99 almost perfect agreement, as proposed by Landis and Koch [27]. However, we need to emphasize that this categorization was originally proposed based on Cohen's Kappa values only.

Data analysis

The data about the performance of SRs on individual AMSTAR and R-AMSTAR domains were presented descriptively as frequencies and percentages. We presented methodological summary scores using median and interquartile range (IQR). Spearman rank correlation was performed to assess the association between total AMSTAR and R-AMSTAR scores.

We used IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, N.Y., USA) and R statistical software and available script files [28] for performing analyses. Statistical significance was defined at $P < 0.05$, two-tailed.

Results

Ninety-seven SRs were included. Table 1 presents a summary description of the included SRs. The references of included studies are presented in Additional file 4, the list of excluded studies in Additional file 5, and the study selection process in Fig. 1.

Methodological quality and adherence to individual AMSTAR and R-AMSTAR domains

The quality ratings of 97 included SRs are presented in Additional file 6 (AMSTAR) and Additional file 7 (R-AMSTAR). The median score was 6 (IQR: 5–8) on AMSTAR and 30 (IQR: 26–35) on R-AMSTAR.

A comparable quality rating was found based on surrogate grades assigned for AMSTAR and R-AMSTAR (Table 2). The lowest grade D was assigned to the majority of included NeuP SRs (64 based on AMSTAR vs. 68 based on R-AMSTAR assessment).

Studies scored best on AMSTAR items 3 (comprehensive literature search, 98% fulfilled), 7 (scientific quality assessed and documented, 89% fulfilled), and 9 (methods used to combine the findings appropriate, 80% fulfilled); and worst on items 11 (conflict of interest included, 12% fulfilled), 1 ('a priori' design provided, 35% fulfilled) and 10 (likelihood of publication bias assessed, 40% fulfilled) (Fig. 2).

When R-AMSTAR was applied (Fig. 3), the best adherence was found for items 3 (comprehensive literature search, 86% of SRs with 4 points), and 2 (duplicate study selection and data extraction, 62% of SRs with 4 points); while the worst adherence was found for items 10 (likelihood of publication bias assessed, 49% of SRs with 1 point), and 8 (scientific quality of the included studies used appropriately in formulating conclusions, 44% of SRs with 1 point).

Table 1 Summary characteristics of 97 included systematic reviews

Characteristic	N of SRs
Year	
1995–2000	4
2001–2005	10
2005–2010	27
2011–2015	56
Number of authors	
1	1
2–5	72
6–10	23
> 10	1
Language of the studies included in SRs	
Any language	49
English	30
English plus other	18
Not reported	6
Language of SRs	
English	91
Chinese	2
French	1
German	1
Spanish	1
Portuguese and English	1
Number of RCTs included	
0–1	8
2–10	37
11–20	30
21–30	14
31–40	4
41–100	3
> 100	1
Number of databases searched	
1	1
2–3	27
4–5	38
> 6	31
Neuropathic pain type	
Peripheral	86
Central	2
Peripheral and central	9
Total number of patients	
0	7
1–1000	28
1001–2000	28
2001–4000	14
> 4001	12
Unclear	8
Meta-analysis	
Yes	65
No	25
Not applicable (empty review)	7
Update of previous SR	
Yes	10
No	87
Number of updates	
1	7
2–3	2
> 4	1
Funding source	
Not reported	35
No external funding	13
Government	12
Foundation	12
None	11
Industry	8
Multiple	6

SR systematic review, *RCT* randomized controlled trial

Methodological quality of Cochrane systematic reviews (CSRs)

The median number of fulfilled items in 31 CSRs was 9 (IQR: 8–10) of 11 on AMSTAR and 37 (IQR: 33–40) of 44 maximum possible R-AMSTAR items.

When surrogate grades were assigned, the majority of CSRs were rated as grade A on AMSTAR ($N = 14$) and R-AMSTAR ($N = 11$). The distribution of other grades was also similar (Table 2).

All CSRs scored "yes" on AMSTAR items 1 ('a priori' design provided) and 3 (comprehensive literature search), and 30 on item 2 (duplicate study selection and data extraction) (Fig. 4). Similar results were found for R-AMSTAR: all CSRs scored 4 points on item 1, 30 on item 3, and 27 on item 2 (Fig. 5).

The worst compliance for CSRs was on AMSTAR item 11, with 18 studies that did not include conflict of interest in both the SR and the included studies (Fig. 4). On R-AMSTAR (Fig. 5), the domains with the poorest performance were domains 9 (appropriate methods used to combine the findings of studies), 10 (likelihood of publication bias assessed), and 8 (scientific quality appropriately used in formulating conclusions).

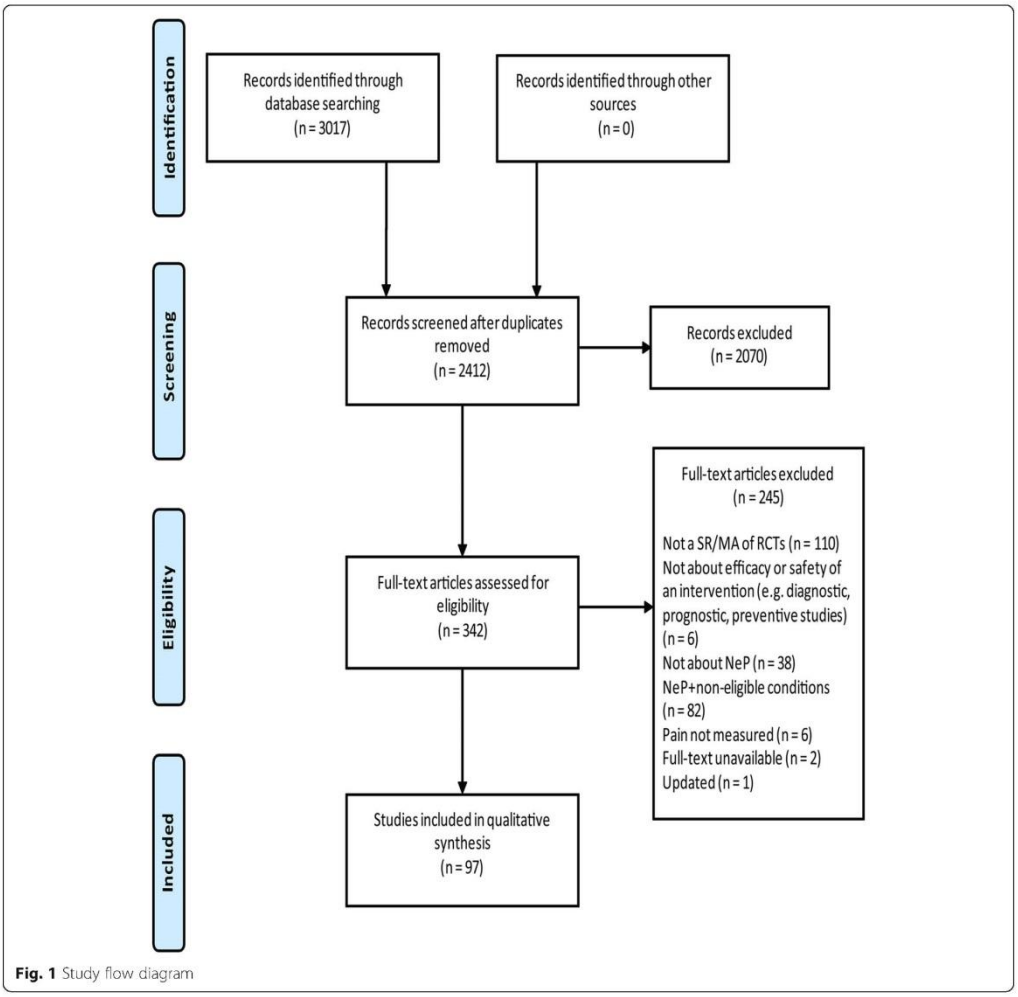

Fig. 1 Study flow diagram

Table 2 Quality of all reviews, Cochrane and non-Cochrane systematic reviews according to AMSTAR and R-AMSTAR percentile scores

	All SRs		Cochrane SRs		Non-Cochrane SRs	
Grade	AMSTAR N (%)	R-AMSTAR N (%)	AMSTAR N (%)	R-AMSTAR N (%)	AMSTAR N (%)	R-AMSTAR N (%)
A	14 (14)	11 (11)	14 (45)	11 (36)	0 (0)	0 (0)
B	9 (9)	9 (9)	6 (19)	6 (19)	3 (5)	3 (5)
C	10 (10)	9 (9)	4 (13)	4 (13)	6 (9)	5 (8)
D	64 (66)	68 (70)	7 (23)	10 (32)	57 (86)	58 (88)
Total	97 (100)	97 (100)	31 (100)	31 (100)	66 (100)	66 (100)

Quality grades assigned according to percentiles (Grade A: ≥90%ile, Grade B: 80–89%ile, Grade C: 70–79%ile, Grade D: ≤ 69%ile)
AMSTAR Assessment of Multiple Systematic Reviews checklist, *R-AMSTAR* a revised version of AMSTAR checklist, *SR* systematic review

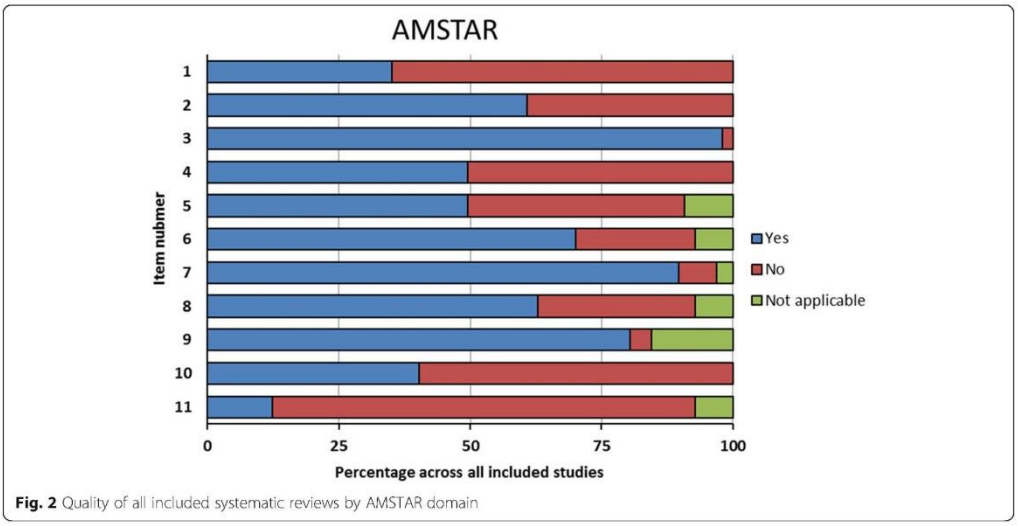

Fig. 2 Quality of all included systematic reviews by AMSTAR domain

Methodological quality of non-Cochrane systematic reviews (NCSRs)

The 66 NCSRs fulfilled a median of 6 (IQR: 5–7) of 11 possible items on AMSTAR and 29 (IQR: 25–32) of maximum 44 items on R-AMSTAR.

As shown in Table 2, none of the NCSRs reached grade A, while the majority received grade D on both AMSTAR ($N = 57$) and R-AMSTAR ($N = 58$). Grading based on the AMSTAR and R-AMSTAR scores yielded almost identical numbers of grade B and C NCSRs.

The NCSRs showed the best compliance with items 3 (comprehensive literature search), 7 (scientific quality of the included studies assessed and documented), and 9 (methods used to combine the findings of studies appropriate) on both AMSTAR (Fig. 6) and R-AMSTAR (Fig. 7). The poorest performing domains on AMSTAR were items

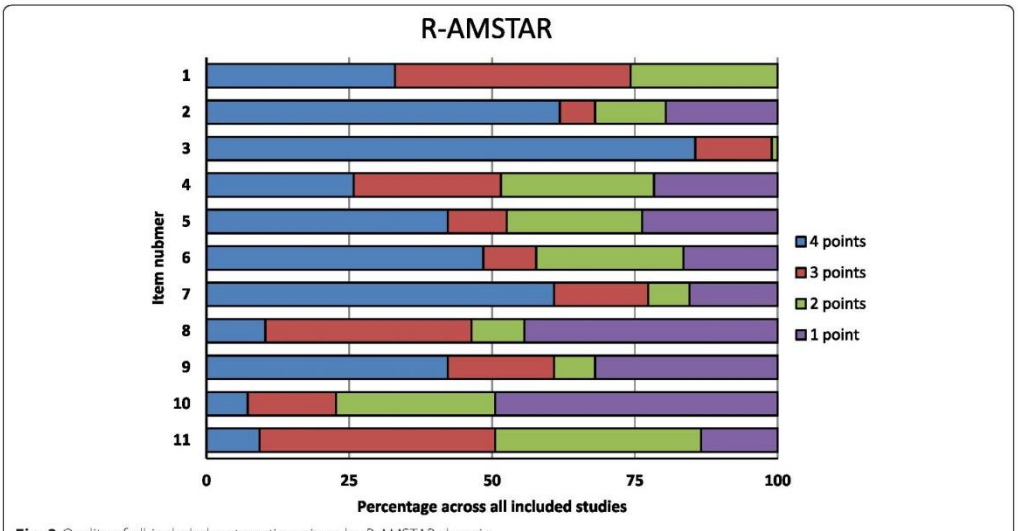

Fig. 3 Quality of all included systematic reviews by R-AMSTAR domain

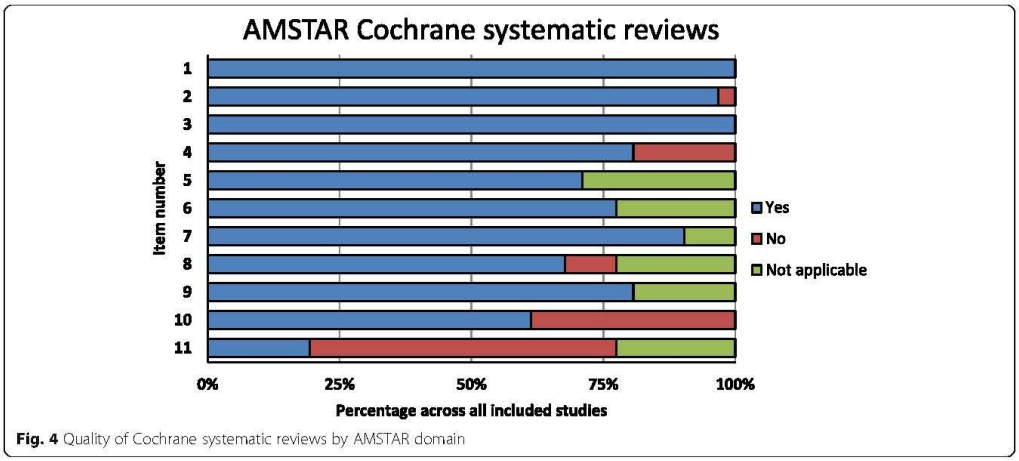

Fig. 4 Quality of Cochrane systematic reviews by AMSTAR domain

1 ('a priori' design provided) and 11 (conflict of interest included), with more than 90% of studies that did not fulfill criteria for a "yes" score (Fig. 6). Figure 7 shows the poorest performing domains on R-AMSTAR: items 10 (likelihood of publication bias assessed) and 8 (scientific quality of the included studies used appropriately in formulating conclusions).

Comparison of methodological quality of Cochrane and non-Cochrane systematic reviews

The quality ratings of 97 SRs expressed in percentiles were similar between AMSTAR (median 47.94, IQR 27.84–71.13) and R-AMSTAR (median 50, IQR 26.3–74.2). Cochrane SRs consistently scored higher than NCSRs, and similar ratings were obtained using both AMSTAR (CSRs median (IQR): 80.93 (71.13–90.72) vs. NCSRs median (IQR): 47.94 (27.84–61.86)) and R-AMSTAR (CSRs median (IQR): 83 (61.3–92.15) vs. NCSRs median (IQR): 42.3 (20.1–57.7)).

Correlation of AMSTAR and R-AMSTAR ratings

We found significant high positive correlation between the AMSTAR and R-AMSTAR scores for all analyzed SRs (Spearman's rho = 0.88, 95% CI 0.83–0.92; $P < 0.001$), as well as for CSRs (Spearman's rho = 0.82, 95% CI 0.65–0.91; $P < 0.001$) and NCSRs (Spearman's rho = 0.75, 95% CI 0.61–0.84; $P < 0.001$).

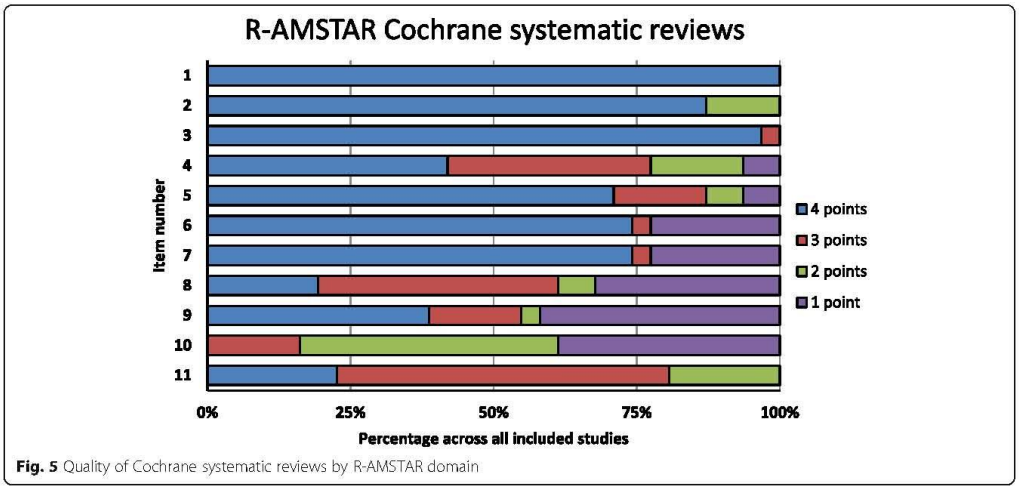

Fig. 5 Quality of Cochrane systematic reviews by R-AMSTAR domain

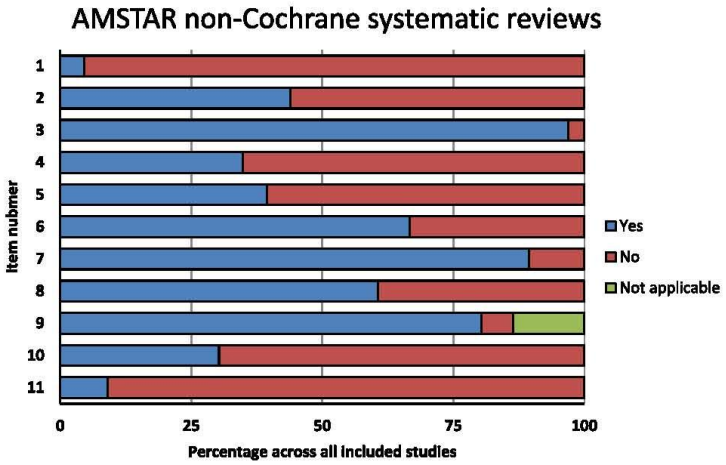

Fig. 6 Quality of non-Cochrane systematic reviews by AMSTAR domain

Interrater agreement

The levels of agreement between the 2 raters on both tools ranged from poor to almost perfect. The overall agreement score was substantial for both AMSTAR (Gwet's AC1 = 0.62, 95%CI 0.39–0.86) and R-AMSTAR (Gwet's AC1 = 0.62, 95%CI 0.53–0.70). Detailed interrater agreement scores for all items on AMSTAR and R-AMSTAR are presented in Tables 3 and 4, respectively.

Four AMSTAR domains reached almost perfect Gwet's AC1 values: 'a priori' design of the research question (item 1), comprehensive literature search (item 3), assessment of the scientific quality of the included studies (item 7), and the use of appropriate methods for combining the findings of studies (item 9). On the other hand, poor agreement was observed when raters judged whether the status of publication was used as an inclusion criterion (item 4) and if the characteristics of the included studies were provided (item 6).

Based on Gwet's AC1 values, items 3, 7, 10 (publication bias assessment) and 11 (information about conflict of interest) had the highest average Gwet's AC1 coefficients (≥0.7), and item 4 the lowest (0.31) on R-AMSTAR.

The assessment of the fulfillment of individual criteria within each R-AMSTAR item showed that poor agreement

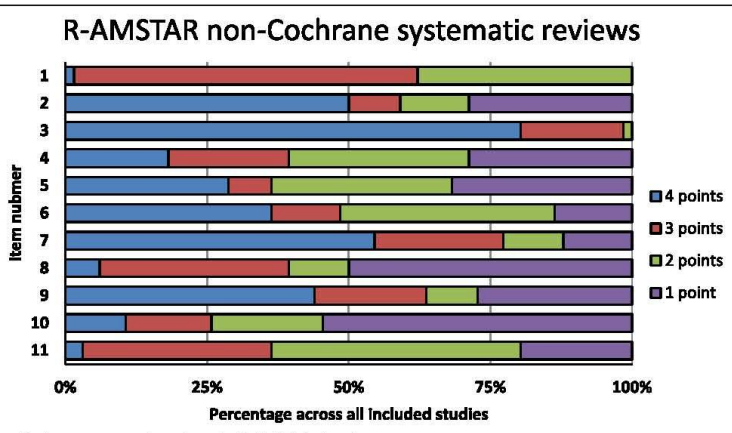

Fig. 7 Quality of non-Cochrane systematic reviews by R-AMSTAR domain

Table 3 Interrater agreement for AMSTAR

Item	Gwet's AC1	SEM	95% CI
1. Was an 'a priori' design provided	0.90	0.04	0.82–0.99
2. Was there duplicate study selection and data extraction	0.47	0.09	0.29–0.66
3. Was a comprehensive literature search performed	0.92	0.03	0.85–0.98
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion	0.03	0.11	−0.19-0.24
5. Was a list of studies (included and excluded) provided	0.63	0.08	0.47–0.79
6. Were the characteristics of the included studies provided	−0.09	0.10	−0.30-0.12
7. Was the scientific quality of the included studies assessed and documented	0.89	0.04	0.81–0.97
8. Was the scientific quality of the included studies used appropriately in formulating conclusions	0.68	0.08	0.53–0.83
9. Were the methods used to combine the findings of studies appropriate	0.88	0.04	0.79–0.96
10. Was the likelihood of publication bias assessed	0.76	0.07	0.62–0.89
11. Was the conflict of interest included	0.80	0.05	0.70–0.91
Overall agreement (mean score of 11 items)	0.62	0.10	0.39–0.86

AMSTAR Assessment of Multiple Systematic Reviews checklist, *SEM* standard error of the mean, *CI* confidence interval

was achieved for criteria 4B (statement of exclusion of any reports based on the publication status, language, etc.) and 1A ('a priori' design provided).

Almost perfect agreement (Gwet's AC1 0.81–1.00) was observed for criteria 1B (statement of inclusion criteria), 3A (at least two electronic sources searched); 3B (reporting years and databases searched), 3E (manual journal search), 5A (Table/list/or figure of included studies provided), 7A ('a priori' methods of assessment of scientific quality provided), 8D (whether clinical consensus statement drives toward revision or confirmation of clinical practice guidelines), 10 C (statistical tests for publication bias assessment), and 11C (conflict of interest assessed in included studies).

Discussion

We found that the methodological quality of analyzed SRs published in the field of NeuP was not optimal. When we compared AMSTAR and R-AMSTAR, we found that, overall, both tools produced comparable quality ratings of the included NeuP SRs.

Several previous studies that focused only on the methodological quality of SRs in other fields of pain used AMSTAR. For example, Martinis et al. assessed the quality of 40 SRs about surgical treatment of low back pain. They reported that 5% of SRs were of excellent quality, most were of fair quality, and 22.5% of poor quality [29]. Song et al. analyzed the methodological quality of 17 SRs on the effectiveness of non-pharmacological cancer pain management and found that only 1 SR was of high quality, while five were of low quality. The mean AMSTAR score was 5.47, indicating overall moderate quality [30]. We could not find any studies that focused only on methodological quality in the field of pain that used R-AMSTAR, and none that compared the use of the 2 measurement tools.

A recent SR of Pieper et al. found that AMSTAR had good measurement properties, but R-AMSTAR did not [31]. Pieper et al. searched four databases to analyze reliability, validity, and feasibility of the AMSTAR and R-AMSTAR. They included 9 studies that analyzed AMSTAR, two studies that analyzed R-AMSTAR, and one article that analyzed both tools. The authors of that SR did not provide any methodological details about calculating interrater reliability for R-AMSTAR because the studies using R-AMSTAR did not report them either [31].

Without any guidance for calculating interrater reliability in the R-AMSTAR, and led by the findings from a study by Wongpakaran et al. that showed Gwet's AC1 coefficient was a more stable interrater reliability measure than Cohen's Kappa in personality disorder samples [32], we decided to use Gwet's AC1 in our study. However, we have to take into account that the interpretation of reliability measures by Landis and Koch was originally published for measures of Cohen's Kappa and it might not be fully applicable for Gwet's AC1 coefficients. Compared to Cohen's Kappa, Gwet's AC1 values tend to be higher [32].

Our results showed poor agreement for AMSTAR item 4 (status of publication was used as an inclusion criterion) and 6 (characteristics of the included studies). Low interrater reliability using Cohen's Kappa coefficient has been previously reported for item 4, and the study mentioned difficulties in applying the publication status item [4].

Findings from a 2015 SR by Pieper et al., based on results from 6 studies, also showed the lowest median interrater reliability using Cohen's Kappa for AMSTAR item 6 (characteristics of the included studies) [31]. Other items with lowest median interrater reliability scores (indicating substantial agreement) were item 8 (scientific quality appropriately used in formulating conclusions) and 5 (list of included and excluded studies), which is in accordance with our interrater reliability measures. The highest interrater

Table 4 Interrater agreement for R-AMSTAR

Item	Criterion	Gwet's AC1	SEM	95% CI
1. Was an 'a priori' design provided	A	0.02	0.11	−0.20-0.24
	B	0.93	0.03	0.88–0.99
	C	0.34	0.10	0.15–0.54
2. Was there duplicate study selection and data extraction	A	0.78	0.06	0.66–0.90
	B	0.64	0.08	0.48–0.79
	C	0.62	0.08	0.45–0.78
3. Was a comprehensive literature search performed	A	0.97	0.02	0.93–1.00
	B	0.94	0.03	0.89–0.99
	C	0.25	0.11	0.03–0.47
	D	0.55	0.09	0.38–0.73
	E	0.83	0.05	0.73–0.93
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion	A	0.55	0.09	0.38–0.72
	B	−0.32	0.10	−0.52-(−0.12)
	C	0.24	0.10	0.04–0.44
	D	0.75	0.07	0.61–0.88
5. Was a list of studies (included and excluded) provided	A	0.95	0.02	0.89–1
	B	0.79	0.06	0.67–0.92
	C	0.41	0.10	0.21–0.60
	D	0.48	0.09	0.30–0.66
6. Were the characteristics of the included studies provided	A	0.79	0.06	0.68–0.91
	B	0.46	0.09	0.28–0.64
	C	0.60	0.08	0.43–0.76
7. Was the scientific quality of the included studies assessed and documented	A	0.86	0.04	0.77–0.95
	B	0.66	0.08	0.50–0.81
	C	0.61	0.08	0.45–0.78
	D	0.73	0.07	0.59–0.86
8. Was the scientific quality of the included studies used appropriately in formulating conclusions	A	0.66	0.08	0.50–0.81
	B	0.23	0.10	0.03–0.43
	C	0.28	0.10	0.07–0.48
	D	0.97	0.02	0.93–1
9. Were the methods used to combine the findings of studies appropriate	A	0.71	0.07	0.57–0.85
	B	0.74	0.07	0.60–0.88
	C	0.68	0.08	0.53–0.83
	D	0.67	0.08	0.52–0.82
	E	0.47	0.10	0.28–0.66
10. Was the likelihood of publication bias assessed	A	0.58	0.08	0.41–0.74
	B	0.80	0.06	0.69–0.92
	C	0.95	0.03	0.90–1
11. Was the conflict of interest included	A	0.70	0.07	0.56–0.84
	B	0.60	0.08	0.44–0.76
	C	0.85	0.05	0.76–0.95
Overall agreement (mean score of 41 items)		0.62	0.04	0.53–0.70

R-AMSTAR, a revised version of Assessment of Multiple Systematic Reviews checklist, *SEM* standard error of the mean, *CI* confidence interval

reliability scores (almost perfect agreement) in the study of Pieper et al. were reported for item 10 (publication bias assessment) and 11 (conflicts of interest stated); those items reached substantial agreement on our sample of 97 SRs [31].

The raters reached substantial agreement on 4 of our R-AMSTAR items with the highest average Gwet's AC1 values (items 3, 7, 10, 11). Compared to Cohen's Kappa values obtained in an SR in subfertility [33], only item 10 in their study had a higher interrater reliability.

For R-AMSTAR we calculated the interrater agreement on 41 items by taking into account all the criteria (from 3 (A-C) to 5 criteria (A-E)) in each of the 11 items. We cannot correctly judge whether the raters agree that the same criteria are fulfilled (e.g., rater 1: A and B; rater 2: C and D) solely by looking into the 11-item based agreement. Our results indicate the most problematic individual criteria within each R-AMSTAR item where our raters obtained poor agreement; they are the statement of exclusion of any reports based on the publication status, language, etc. (criterion 4B) and 'a priori' design provided (criterion 1A). These items would particularly benefit from further clarification on how to apply them.

We also confirmed in our sample of NeuP interventional SRs that CSRs have a higher methodological quality compared to NCSRs: the majority of CSRs had scores above the 80th percentile, compared to NCSRs where the majority scored in the lowest category. A number of studies from different research fields have previously shown that the quality of CSRs is superior [4, 8, 34–36]. However, we did not find a difference in correlation measures between AMSTAR and R-AMSTAR depending on whether it is a Cochrane review or not. In the study of Popovich et al., a much higher correlation between AMSTAR and R-AMSTAR was found for NCSRs than for CSRs in the field of subfertility. These results warrant further studying [31].

In order to improve the methodological quality of SRs, a joint action by SR authors, peer reviewers, and editors is needed. When planning and reporting their SR, the authors should follow a relevant checklist to ensure that the manuscript has appropriate methodological quality. Peer reviewers should analyze SRs against the relevant checklist, and editors could endorse methodological quality tools for specific article types and require authors to adhere to them. Editors are gatekeepers who can make sure the authors adhere to expected submission criteria. A recent editorial described that one journal is beginning this process: inspired by the findings of a study that showed poor and stagnating methodological quality of SRs in the field of urology [37], the BJU International decided to request from all SR authors to submit an AMSTAR checklist together with the manuscript, which will be utilized as part of the editorial and peer-review process [38].

A limitation of this study is that we have included SRs published since 1995, while AMSTAR was only published in 2007. It is possible that the methodological quality of SRs has increased since the introduction of AMSTAR since there is already some evidence that might support this [39–42]. Another limitation of this study is that calculating AMSTAR scores in this way implies that each item has the same weight. This assumption might be wrong because not all the domains of AMSTAR should have the same methodological value.

It is also possible that the differences observed between interrater agreement results obtained in ours and other studies might be influenced by the experience of the raters [43], although this is difficult to judge since rater experience is not frequently reported in the included studies [31]. We believe that both tools could be easily applied by an untrained person after a thorough discussion of the items and a calibration exercise before assessment, as we did.

Future studies should also include an assessment of ROBIS, a new tool for assessing the risk of bias in SRs, which was published in 2016 [44]. Likewise, the development of AMSTAR 2 was announced at the 2016 Cochrane Colloquium [45], so new studies about the updated tool are warranted once it is published.

Conclusion

In conclusion, since both AMSTAR and R-AMSTAR tools produced comparable quality ratings of the included SRs, we advise future use of AMSTAR because it is shorter and it has been shown to have good measurement properties in previous studies, unlike R-AMSTAR. Our analysis indicated that the methodological quality of existing SRs about interventions for the management NeuP is suboptimal, which calls for improvement by better adherence to methodological quality criteria.

Additional files

Additional file 1: Search strategy for MEDLINE. (DOCX 23 kb)

Additional file 2: Interrater agreement (Cohen's kappa) for AMSTAR. (DOCX 22 kb)

Additional file 3: Interrater agreement (Cohen's kappa) for R-AMSTAR. (DOCX 28 kb)

Additional file 4: References of included studies. (DOCX 139 kb)

Additional file 5: List of excluded studies with reasons. (DOCX 296 kb)

Additional file 6: AMSTAR rating for each study. (DOCX 211 kb)

Additional file 7: R-AMSTAR rating for each study. (DOCX 221 kb)

Abbreviations

AC1: Gwet's AC1 interrater agreement coefficient; AMSTAR: The Assessment of Multiple Systematic Reviews; CSR: Cochrane systematic review; IASP: International Association for the Study of Pain; IQR: Interquartile range;

MeSH: Medical Subject Headings; NCSR: Non-Cochrane systematic review; NeuP: Neuropathic pain; PROSPERO: International prospective register of systematic reviews; R-AMSTAR: Revised AMSTAR; RCT: Randomized controlled trial; ROBIS: Tool to assess risk of bias in systematic reviews; SR: Systematic review

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
LP conceived the study design and helped to resolve discrepancies. AJK and SD independently screened and included eligible studies. KV and NM performed methodological quality assessments. DP and SD performed statistical analyses. SD drafted the manuscript with the help of LP. All authors were involved in critical revision of the manuscript, read and approved the final version of the manuscript, and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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6 DODATCI

Dodatak 1. Strategija pretraživanja korištena za pretraživanje elektroničke baze podataka MEDLINE.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present (27.02.2015.)

1 exp Neuralgia/

2 Neuropathic pain$.mp

3 (neuropath$3 adj5 pain$).mp.

4 Neuropath$3.mp.

5 neuralg$.mp.

6 (neurogen$ adj3 pain$).mp.

7 Neurodyni$.mp.

8 Nerve pain.mp

9 pain nerve.mp.

10 Diabetic Neuropathies/

11 (diabet$ adj3 neuropath$3).mp.

12 (postherp$ adj3 neuralg$).mp.

13 (trigemin$ adj3 neuralg$).mp.

14 ((facial$ or face) adj3 (pain$ or neuralg$)).mp.

15 Burning Mouth Syndrome/

16 (burning adj3 mouth$).mp.

17 (HIV adj3 neuropath$3).mp.

18 (neuropath$3 adj3 cancer$ adj3 pain$).mp.

19 (pain$ adj3 neuropath$3 adj3 (post-treatment$ or post treatment$ or posttreatment$ or surg$ or post-op$ or postop$ or post op$)).mp.

20 Phantom limb/

21 (phantom adj3 limb$).mp.

22 Polyneuropathies/

23 (pain$ adj3 polyneuropath$3).mp.

24 exp Nerve Compression Syndromes/

25 exp Peripheral Nervous System Diseases/

26 ((compress$ or peripher$) adj3 (Neuropath$3 or nerv$)).mp.

27 Spinal Cord Injuries/

28 (spinal cord adj3 (injury or injuries or injured)).mp.

29 ((post amputation or post-amputation or postamputation) adj3 pain$).mp.

30 (stroke$ adj3 pain$).mp.

31 (idiopathic$ adj3 (pain$ or Neuropath$3)).mp.

32 exp Multiple Sclerosis/

33 multiple sclerosis.mp.

34 Stroke/

35 Radiculopathy/

36 (radiculopath$ or radicular pain$).mp.

37 exp Complex regional pain syndromes/

38 (complex adj3 region$ adj3 pain$).mp.

39 CRPS.mp.

40 (hand$ adj3 shoulder$ adj3 syndrom$).mp.

41 causalgi$.mp.

42 pain$.mp.

43 (4 or 10 or 15 or 16 or 20 or 22 or 24 or 25 or 27 or 28 or 32 or 33 or 34 or 40) and 42

44 1 or 2 or 3 or 5 or 6 or 7 or 8 or 9 or 11 or 12 or 13 or 14 or 17 or 18 or 19 or 21 or 23 or 26 or 29 or 30 or 31 or 35 or 36 or 37 or 38 or 39 or 41

45 43 or 44

46 Hyperalgesi$.mp.

47 allodynia$.mp.

48 46 or 47

49 45 or 48

50 (review or review,tutorial or review, academic).pt.

51 (medline or medlars or embase or pubmed or cochrane).tw,sh.

52 (scisearch or psychinfo or psycinfo).tw,sh.

53 (psychlit or psyclit).tw,sh.

54 cinahl.tw,sh.

55 ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.

56 (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.

57 (pooling or pooled or mantel haenszel).tw,sh.

58 (peto or dersimonian or der simonian or fixed effect).tw,sh.

59 (retraction of publication or retracted publication).pt.

60 or/51-59

61 50 and 60

62 meta-analysis.pt.

63 meta-analysis.sh.

64 (meta-analys$ or meta analys$ or metaanalys$).tw,sh.

65 (systematic$ adj5 review$).tw,sh.

66 (systematic$ adj5 overview$).tw,sh.

67 (quantitativ$ adj5 review$).tw,sh.

68 (quantitativ$ adj5 overview$).tw,sh.

69 (quantitativ$ adj5 synthesis$).tw,sh.

70 (methodologic$ adj5 review$).tw,sh.

71 (methodologic$ adj5 overview$).tw,sh.

72 (integrative research review$ or research integration).tw.

73 or/62-72

74 61 or 73

75 Comment/

76 Letter/

77 Editorial/

78 Guideline/

79 or/75-78

80 74 not 79

81 49 and 80

82 remove duplicates from 81

Dodatak 2. Upitnik korišten za procjenu primjerenosti ključnih ishoda u sustavnim pregledima o intervencijama za neuropatsku bol.

Opće karakteristike:

*Molimo zaokružite vaš spol:
Muško Žensko

*Molimo navedite svoje zanimanje:
Kliničar
Istraživač
Metodolog
Statističar
Ostalo: _____

*Molimo navedite koliko ste dugo uključeni u svoje istraživačko područje u polju kronične boli?
Manje od 5 godina
Između 6-10 godina
Između 11-20 godina
Više od 21 godinu

*Je li vaše istraživanje (randomizirani kontrolirani pokus ili sustavni pregled) o kroničnoj boli provedeno prije siječnja 2005.?
Da Ne

* Jeste li registrirali protokol istraživanja prije početka istraživanja?
Da Ne

*Jeste li bili uključeni u razvoj ključnog skupa ishoda u određenom istraživačkom području (bilo IMMPACT inicijative ili neke druge organizacije)?
Da Ne
Sada ćemo vam postaviti nekoliko pitanja o domenama ishoda i mjerama ishoda. Domena ishoda je izraz koji označava ono što je mjereno (npr. bol). Mjera ishoda odnosi se na mjerni

instrument, tj. kako je određeni ishod mjeren (npr. vizualno analogna ljestvica, numerička ljestvica).

1. Jeste li čuli do sada za ključni skup domena ishoda za procjenu učinkovitosti i sigurnosti intervencija za kroničnu bol kojeg je preporučila IMMPACT inicijativa?
Da Ne
(ako je odgovor Ne, prelazi se na 3. pitanje)

2. Koliko domena ishoda sadrži ključni skup kojeg preporučuje IMMPACT inicijativa?
4 6 8 10

3. Koje od ovih domena ishoda preporučuje IMMPACT inicijativa kao dio ključnog skupa ishoda za kroničnu bol (označite sve što mislite da je primjenjivo):
Bol
Fizička funkcija
Emocionalno funkcioniranje
Ispitanikova ocjena poboljšanja i zadovoljstvo terapijom
Simptomi i nuspojave
Dispozicija ispitanika
Kliničarova ili surogatna ocjena globalnog poboljšanja
Funkcioniranje u ulozi (t.j. posao, edukacija)
Farmakoekonomske mjere i korištenje zdravstvene skrbi
Biološki markeri (t.j. procjena na temelju kvantitativnog senzornog testiranja, slikovne dijagnostike, genskih markera, farmakogenomike, biopsija kože)
Dodatna analgezija
Stanje bez boli
Spavanje
Interpersonalno funkcioniranje
Nošenje s bolešću
Neuropsihološka procjena kognitivne i motorne funkcije
Patnja i drugi problemi pri kraju života

4. Molimo ocijenite ljestvicom od 1 do 9 (1=nevažno, 9=apsolutno nužno) primjerenost sljedećih domena ishoda za uključenje u ključni skup ishoda za procjenu intervencija o kroničnoj boli:

Bol

Fizička funkcija

Emocionalno funkcioniranje

Ispitanikova ocjena poboljšanja i zadovoljstvo terapijom

Simptomi i nuspojave

Dispozicija ispitanika

Kliničarova ili surogatna ocjena globalnog poboljšanja

Funkcioniranje u ulozi (t.j. posao, edukacija)

Farmakoekonomske mjere i korištenje zdravstvene skrbi

Biološki markeri (t.j. procjena na temelju kvantitativnog senzornog testiranja, slikovne dijagnostike, genskih markera, farmakogenomike, biopsija kože)

Dodatna analgezija

Stanje bez boli

Spavanje

Interpersonalno funkcioniranje

Nošenje s bolešću

Neuropsihološka procjena kognitivne i motorne funkcije

Patnja i drugi problemi pri kraju života

5. Prilikom izrade vašeg sustavnog pregleda/randomiziranog kontroliranog pokusa o neuropatskoj boli, jeste li koristili ključne domene ishoda preporučene od strane IMMPACT inicijative?

Da djelomično Ne Nije primjenjivo (istraživanje je provedeno prije objave IMMPACT ključnog skupa ishoda 2003. godine)

6. Pretraživanjem literature pronašli smo velik broj sustavnih pregleda u kojima se procjenjuju intervencije za ublažavanje neuropatske boli, ali samo mali dio (9/81) tih sustavnih pregleda objavljenih nakon 2003. (nakon objave preporuke IMMPACT inicijative) je imao sve ključne domene ishoda koje IMMPACT preporučuje za kroničnu bol. Možete li navesti neke razloge zbog kojih niste koristili preporučene ishode; ili probleme koje ste vi

iskusili ili za koje smatrate da bi mogli postojati, a koji onemogućuju dosljedno korištenje svih domena ishoda koje preporučuje IMMPACT?

Nedovoljno poznavanje preporučenih domena ishoda
Preporučene domene ishoda nisu bile relevantne/primjerene istraživanju
Preporučene domene ishoda bilo je teško primijeniti
Prekomjerno opterećenje ispitanika
Ograničeni resursi autora istraživanja (ljudstvo, financiranje, vrijeme)
Korištenje ključnih domena ishoda nije bilo obvezno za objavljivanje protokola ili rada u časopisu
Nepostojanje smjernica o preporučenim domenama ishoda u istraživanjima o kroničnoj boli od regulatornih agencija (kao što su Američka Agencija za hranu i lijekove- FDA, Europske Agencija za Lijekove- EMA)
Drugi ishodi bili su primjereniji istraživanju
Ključne domene ishoda nisu bile korištene u primarnim studijama (odnosi se na autore sustavnih pregleda)
Ostalo, navedite:

7. Molimo izaberite među ponuđenim domenama ishoda one koje biste vi osobno definirali kao ključne i time bi trebale biti dio ključnog skupa ishoda za procjenu učinkovitosti i sigurnosti intervencija za ublažavanje kronične boli:
Bol
Fizička funkcija
Emocionalno funkcioniranje
Ispitanikova ocjena poboljšanja i zadovoljstvo terapijom
Simptomi i nuspojave
Dispozicija ispitanika
Kliničarova ili surogatna ocjena globalnog poboljšanja
Funkcioniranje u ulozi (t.j. posao, edukacija)
Farmakoekonomske mjere i korištenje zdravstvene skrbi
Biološki markeri (t.j. procjena na temelju kvantitativnog senzornog testiranja, slikovne dijagnostike, genskih markera, farmakogenomike, biopsija kože)
Dodatna analgezija
Stanje bez boli

Spavanje
Interpersonalno funkcioniranje
Nošenje s bolešću
Neuropsihološka procjena kognitivne i motorne funkcije
Patnja i drugi problemi pri kraju života
Nešto drugo: _____

8. Jeste li čuli do sada za ključne mjere ishoda (mjerne instrumente ishoda) za kroničnu bol kojeg je preporučila IMMPACT inicijativa 2005. godine?
Da Ne

9. Koje od ovih mjera ishoda za procjenu učinkovitosti i sigurnosti intervencija za ublažavanje kronične boli preporučuje IMMPACT inicijativa kao ključne (označite sve što mislite da je primjenjivo):
Numerička ljestvica za procjenu intenziteta boli (0-10)
Upotreba dodatnih analgetika
Verbalna ljestvica za procjenu intenziteta boli (bez boli, blaga,umjerena, jaka bol) - VRS
Multidimenzionalni inventar boli (MPI) - ljestvica interferencije
Kratki popis boli (BPI) – interferencija
Beckov inventar depresije (BDI)
Profila stanja raspoloženja (POMS)
Ispitanikova globalna procjena promjene
Prijava spontano zabilježenih nuspojava liječenja i simptoma i upotreba otvorenih podsjetnika
Detaljni prikaz podataka o uključivanju ispitanika i tijeku ispitanika kroz istraživanje, uključujući sve informacije navedene u CONSORT smjernicama
Skraćeni oblik McGill upitnika o boli (SF-MPQ)
Vizualno analogna ljestvica za procjenu intenziteta boli (0-100 mm ili 0-10 cm)
Upitnik zdravstvenog statusa SF-36
Gracely ljestvica za bol
West-Haven Yale Multidimenzionalni inventar boli
Ljestvica za neuropatsku bol (NPS)
Upitnik za procjenu neuropatskih simptoma NTSS-6
Upitnik zdravstvenog statusa SF-12

Upitnik EQ-5D za procjenu kvalitete života
Registar za stanje i karakteristike anksioznosti (STAI)
Ocjena globalnog učinka (GPE)
Kliničarova globalna procjena promjene (CGIC)
Profil učinka bolesti
Skala bolničke anksioznosti i depresije (HADS)
Potreba za kirurškim zahvatom kao mjera učinkovitosti konzervativnog liječenja
Stopa povrata bolesti

10. Molimo vaše mišljenje: ocijenite ljestvicom od 1 do 9 (1=nevažno, 9=apsolutno nužno) primjerenost sljedećih mjera ishoda za uključenje u ključni skup mjera ishoda za procjenu učinkovitosti i sigurnosti intervencija za kroničnu bol:
Numerička ljestvica za procjenu intenziteta boli (0-10)
Upotreba dodatnih analgetika
Verbalna ljestvica za procjenu intenziteta boli (bez boli, blaga,umjerena, jaka bol) - VRS
Multidimenzionalni inventar boli (MPI) - ljestvica interferencije
Kratki popis boli (BPI) – interferencija
Beckov inventar depresije (BDI)
Profila stanja raspoloženja (POMS)
Ispitanikova globalna procjena promjene
Prijava spontano zabilježenih nuspojava liječenja i simptoma i upotreba otvorenih podsjetnika
Detaljni prikaz podataka o uključivanju ispitanika i tijeku ispitanika kroz istraživanje, uključujući sve informacije navedene u CONSORT smjernicama
Skraćeni oblik McGill upitnika o boli (SF-MPQ)
Vizualno analogna ljestvica za procjenu intenziteta boli (0-100 mm ili 0-10 cm)
Upitnik zdravstvenog statusa SF-36
Gracely ljestvica za bol
West-Haven Yale Multidimenzionalni inventar boli
Ljestvica za neuropatsku bol (NPS)
Upitnik za procjenu neuropatskih simptoma NTSS-6
Upitnik zdravstvenog statusa SF-12
Upitnik EQ-5D za procjenu kvalitete života
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Ocjena globalnog učinka (GPE)
Kliničarova globalna procjena promjene (CGIC)
Profil učinka bolesti
Skala bolničke anksioznosti i depresije (HADS)
Potreba za kirurškim zahvatom kao mjera učinkovitosti konzervativnog liječenja
Stopa povrata bolesti

11. Prilikom izrade vašeg sustavnog pregleda/randomiziranog kontroliranog pokusa o neuropatskoj boli, jeste li koristili ključne mjere ishoda preporučene od strane IMMPACT inicijative?
Da Djelomično Ne Nije primjenjivo (istraživanje je provedeno prije objave IMMPACT ključnog skupa ishoda 2005. godine)

12. Možete li navesti neke razloge zbog kojih niste koristili preporučene ključne mjere ishoda; ili probleme koje ste iskusili ili za koje smatrate da bi mogli postojati, a koji onemogućuju dosljedno korištenje ključnih mjera ishoda koje preporučuje IMMPACT?
Nedovoljno poznavanje preporučenih ključnih mjera ishoda
Mjere ishoda nisu bile relevantne/primjerene istraživanju
Mjere ishoda nisu pouzdane (engl. reliable)
Mjere ishoda nisu osjetljive na promjenu (engl. responsiveness)
Mjere ishoda bilo je teško primijeniti
Prekomjerno opterećenje ispitanika
Ograničeni resursi (ljudstvo, financiranje, vrijeme)
Mjere ishoda nisu bile obvezne za objavljivanje protokola ili rada u časopisu
Nepostojanje smjernica o preporučenim mjerama ishoda u istraživanjima o kroničnoj boli od regulatornih agencija (kao što su Američka Agencija za hranu i lijekove- FDA, Europske Agencija za Lijekove- EMA)
Druge mjere ishoda bile su primjerenije istraživanju
Mjere ishoda nisu bile korištene u primarnim studijama (odnosi se na autore sustavnih pregleda)
Ostalo, navedite:

13. Molimo izaberite među ponuđenim mjerama ishoda one koje biste vi osobno definirali kao ključne za procjenu učinkovitosti i sigurnosti intervencija za ublažavanje kronične boli:

Numerička ljestvica za procjenu intenziteta boli (0-10)
Upotreba dodatnih analgetika
Verbalna ljestvica za procjenu intenziteta boli (bez boli, blaga,umjerena, jaka bol) - VRS
Multidimenzionalni inventar boli (MPI) - ljestvica interferencije
Kratki popis boli (BPI) – interferencija
Beckov inventar depresije (BDI)
Profila stanja raspoloženja (POMS)
Ispitanikova globalna procjena promjene
Prijava spontano zabilježenih nuspojava liječenja i simptoma i upotreba otvorenih podsjetnika
Detaljni prikaz podataka o uključivanju ispitanika i tijeku ispitanika kroz istraživanje, uključujući sve informacije navedene u CONSORT smjernicama
Skraćeni oblik McGill upitnika o boli (SF-MPQ)
Vizualno analogna ljestvica za procjenu intenziteta boli (0-100 mm ili 0-10 cm)
Upitnik zdravstvenog statusa SF-36
Gracely ljestvica za bol
West-Haven Yale Multidimenzionalni inventar boli
Ljestvica za neuropatsku bol (NPS)
Upitnik za procjenu neuropatskih simptoma NTSS-6
Upitnik zdravstvenog statusa SF-12
Upitnik EQ-5D za procjenu kvalitete života
Registar za stanje i karakteristike anksioznosti (STAI)
Ocjena globalnog učinka (GPE)
Kliničarova globalna procjena promjene (CGIC)
Profil učinka bolesti
Skala bolničke anksioznosti i depresije (HADS)
Potreba za kirurškim zahvatom kao mjera učinkovitosti konzervativnog liječenja
Stopa povrata bolesti
Nešto drugo: _____

14. Biste li u budućim istraživanjima koristili ključni skup ishoda i ključne mjere ishoda koje definira IMMPACT inicijativa za kroničnu bol?

Da Možda Ne

15. Što bi vas potaklo da u budućnosti koristite ključni skup ishoda i ključne mjere ishoda koje definira IMMPACT inicijativa za kroničnu bol?

Lakše dizajniranje novog istraživanja
Lakše uspoređivanje rezultata različitih istraživanja
Lakše provođenje sustavnog pregleda/meta-analize zbog postojanja homogenih ishoda u primarnim studijama
Lakša procjena kliničke učinkovitosti ispitivanih intervencija
Smanjenje pristranosti zbog neprijavljivanja ishoda (engl. outcome reporting bias)
Smanjenje količine nekvalitetnog istraživanja (engl. research waste)
Obaveza navođenja ključnog skupa ishoda pri registraciji protokola istraživanja
Obaveza navođenja razloga za nekorištenjem pojedinog ishoda iz ključnog skupa ishoda pri registraciji protokola istraživanja (ukoliko ishodi nisu primjenjivi za istraživanje)
Postojanje smjernica o preporučenim domenama i mjerama ishoda u istraživanjima o kroničnoj boli od regulatornih agencija (kao što su Američka Agencija za hranu i lijekove- FDA, Europske Agencija za Lijekove- EMA)
Ostalo, navedite: _____

Ako imate bilo kakav komentar vezano za ovo istraživanje, postavljena pitanja ili ključni skup ishoda koje definira IMMPACT inicijativa, molimo navedite:

Ako želite dobiti rezultate istraživanja nakon što istraživanje završimo, molimo ostavite svoju adresu e-pošte. Pritom naglašavamo da to nije nužno i da je anketa inače zamišljena kao anonimna.

Hvala Vam na sudjelovanju u istraživanju.