Bijlagedocument
Richtlijn Chronische Jeuk 2022

Nederlandse Vereniging voor Dermatologie en Venereologie

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Inhoudsopgave

Bijlage 1: Verantwoording

Geldigheid

Bij het opstellen van de richtlijn heeft de werkgroep per module een inschatting gemaakt over de maximale termijn waarop herbeoordeling moet plaatsvinden en eventuele aandachtspunten geformuleerd die van belang zijn bij een toekomstige herziening (update). De Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV) is regiehouder van deze richtlijn chronische jeuk herziening 2022 en eerstverantwoordelijke op het gebied van de actualiteitsbeoordeling van de richtlijn chronische jeuk herziening 2022. De andere aan deze richtlijn deelnemende wetenschappelijke verenigingen of gebruikers van de richtlijn delen de verantwoordelijkheid en informeren de regiehouder over relevante ontwikkelingen binnen hun vakgebied.

Doel en doelgroep

Doel

Deze richtlijn over chronische jeuk is een document met aanbevelingen ter ondersteuning van de dagelijkse praktijkvoering. De richtlijn berust op de resultaten van wetenschappelijk onderzoek en aansluitende meningsvorming gericht op het vaststellen van goed medisch handelen. De richtlijn geeft aanbevelingen voor de diagnostiek, begeleiding, behandeling en follow-up van patiënten met chronische jeuk.

Doelgroep

De richtlijn is bedoeld voor alle betrokken beroepsgroepen. Voor huisartsen geldt primair de NHG-Standaard. Als de huisarts bij patiënten met chronische jeuk niet meer met de NHG-Standaard uitkomt, kan de huisartsen gebruikmaken van deze richtlijn. Voor patiënten zijn afgeleide producten gemaakt, zoals te vinden op de websites van de betrokken patiëntenvereniging(en) en op www.thuisarts.nl.

Samenstelling werkgroep

Voor het ontwikkelen van de richtlijn is in 2019 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen die betrokken zijn bij de zorg voor patiënten met chronische jeuk en patiëntenvertegenwoordiger(s), vanuit het HPN (zie hiervoor het overzicht van de werkgroepleden de tabel hieronder). Wetenschappelijke verenigingen zoals NVDV, NVVN, NHG, NVKG, NVK, NIP, NVH, V&VN en HPN en stakeholders zoals VIG, NVZ, V&VN, KNMP, NFU, ZN, ZiNL en de patiëntenfederatie werden voor de knelpunten analyse en commentaarronde uitgenodigd.

De werkgroepleden zijn door hun beroepsverenigingen gemandateerd voor deelname. De werkgroep is verantwoordelijk voor de integrale tekst van deze richtlijn.

Werkgroepleden

Werkgroeplid	Affiliatie en vereniging
Dhr. Dr. H.B. Thio, dermatoloog, (voorzitter)	Erasmus MC, Rotterdam, NVDV
Dhr. Dr. D.M.W. Balak, dermatoloog	UMC Utrecht, NVDV
Dhr. Drs. Z. Çiftçi (secretaris) (vanaf februari 2020)	Bureau NVDV, Utrecht, NVDV
Dhr. Drs. T. Boere (secretaris) (tot februari 2020)	Bureau NVDV, Utrecht, NVDV
Mw. Dr. M.C. Bolling, dermatoloog	UMC Groningen, NVDV
Dhr. Dr. J.J.E. van Everdingen, dermatoloog n.p.	Directeur NVDV, Utrecht
Dhr. Dr. R.A. Faaij, klinisch geriater	Diakonessenhuis, Utrecht, NVKG
Dhr. Drs. P.M.J.H. Kemperman, dermatoloog	Amsterdam UMC & Dijklander ziekenhuis, Purmerend, NVDV
Mw. Drs. T.A. Kouwenhoven, dermatoloog i.o.	Radboudumc. Nijmegen, NVDV
Dhr. Drs. A.S.H.J. Lokin, dermatoloog i.o.	Amsterdam UMC, NVDV
Mw. Drs. H. Heineman, huisarts	Groningen, NHG

Mw. L. Meerkerk, verpleegkundig specialist	Haaglanden MC, den Haag, V&VN
Mw. Drs. H. Rijk-van Gent, kinderarts	Antonius ziekenhuis, Sneek, NVK
Dhr. Dr. R. Rosken, internist-allergoloog-immunoloog	Zaans Medisch Centrum, NVvAKI
Mw. Dr. M.E. Schram, dermatoloog	ZBC Multicare, Hilversum, NVDV
Mw. Dr. S. Spillekom- van Koulil, psycholoog	Radboud UMC, Nijmegen, NIP
Mw. Drs. M. Stolting (secretaris) (vanaf september 2021)	Bureau NVDV, Utrecht, NVDV
Mw. E. Swanborn	Voorzitter HPN

Belangenverklaringen

De KNMG-code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden hebben bij aanvang van en na het afronden van de richtlijn schriftelijk verklaard of zij in de laatste twee jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatiemanagement, kennisvalorisatie) hebben gehad. Een overzicht van de belangen van werkgroepleden en het oordeel over het omgaan met eventuele belangen is opgenomen in bijlage 3. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van de NVDV.

Inbreng patiëntenperspectief

Er is aandacht besteed aan het patiëntenperspectief doordat er patiëntenvertegenwoordigers zitting hadden in de werkgroep (zie ook samenstelling van de werkgroep). De conceptrichtlijn is tevens voor commentaar voorgelegd aan HPN.

Wkkgz & Kwalitatieve raming van mogelijke substantiële financiële gevolgen

Bij de richtlijn is conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uitgevoerd of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling zijn richtlijnmodules op verschillende domeinen getoetst (gebaseerd op het stroomschema ontwikkeld door FMS).

Uit de kwalitatieve raming blijkt dat er waarschijnlijk geen substantiële financiële gevolgen zijn, zie onderstaande tabel.

Module	Uitkomst Raming	Toelichting
Diagnostiek	Geen substantiële financiële gevolgen	n.v.t.
Lokale therapie	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbevelingen breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft, het geen toename in het aantal in te zetten voltijdsequivalenten aan zorgverleners betreft en het geen wijziging in het opleidingsniveau van zorgpersoneel betreft. Er worden daarom geen financiële gevolgen verwacht.
Systemische therapie	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbevelingen breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening

		betreft, het geen toename in het aantal in te zetten voltijdsequivalenten aan zorgverleners betreft en het geen wijziging in het opleidingsniveau van zorgpersoneel betreft. Er worden daarom geen financiële gevolgen verwacht.
Psychologische behandeling	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbevelingen breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft, het geen toename in het aantal in te zetten voltijdsequivalenten aan zorgverleners betreft en het geen wijziging in het opleidingsniveau van zorgpersoneel betreft. Er worden daarom geen financiële gevolgen verwacht.
Therapie bij specifieke subgroepen	Geen substantiële financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbevelingen breed toepasbaar zijn (>40.000 patiënten), volgt uit de toetsing dat het geen nieuwe manier van zorgverlening of andere organisatie van zorgverlening betreft, het geen toename in het aantal in te zetten voltijdsequivalenten aan zorgverleners betreft en het geen wijziging in het opleidingsniveau van zorgpersoneel betreft. Er worden daarom geen financiële gevolgen verwacht.

Implementatie

In de verschillende fasen van de richtlijnontwikkeling is rekening gehouden met de implementatie van de richtlijn(module) en de praktische uitvoerbaarheid van de aanbevelingen. Daarbij is uitdrukkelijk gelet op factoren die de invoering van de richtlijn in de praktijk kunnen bevorderen of belemmeren De richtlijn wordt via het internet verspreid onder alle relevante beroepsgroepen en ziekenhuizen en er zal in verschillende specifieke vaktijdschriften aandacht worden besteed aan de richtlijn. Tevens zal een samenvatting worden gemaakt. Het volledige implementatieplan is opgenomen in het bijlagedocument.

Werkwijze

De werkgroep chronische jeuk heeft in 2019-2021 de vraag- en doelstellingen van deze richlijn met elkaar afgestemd en uitgewerkt. De ontwikkeling van deze richtlijn is gebaseerd op de European S2k Guideline on Chronic Pruritus van the European Dermatology Forum (EDF) en the European Academy of Dermatology and Venereology (EADV).
Hieronder wordt de werkwijze van de richtlijn 2021 verder toegelicht.
Ten tijde van het tot stand komen van de richtlijnwerkgroep chronische jeuk waren enkele nieuwe, belangrijke publicaties verschenen die hoofdzakelijk als bouwsteen hebben gediend bij het opstellen van deze richtlijn.

Hoofdzakelijk gaat het hier om de European S2k Guideline on Chronic Pruritus van the European Dermatology Forum (EDF) en the European Academy of Dermatology and Venereology (EADV) uit 2019. Daar de Europese werkgroep in hun richtlijn met algemene literatuur zoekacties heeft gezocht naar wetenschappelijke onderbouwing van de uitgangsvragen over de algehele klinische benadering van de patiënt met chronische jeuk, is er door de Nederlandse richtlijnwerkgroep besloten om niet hetzelfde pad te bewandelen en om de focus en de middelen van wetenschappelijke onderbouwing toe te spitsen op enkele belangrijke aspecten van de behandeling van CP. Hiervoor heeft de werkgroep bij de eerste vergadering een selectie gemaakt van 6 verschillende behandelmethoden/interventies welke uitvoerig zijn uitgezocht middels systematische literatuur zoekacties en beoordeling van de methodologische kwaliteit middels de GRADE-methode.

AGREE

Deze richtlijn is opgesteld conform de eisen vermeld in het rapport Medisch Specialistische Richtlijnen 2.0 van de adviescommissie Richtlijnen van de Raad Kwaliteit. [Medisch Specialistische Richtlijnen] Dit rapport is gebaseerd op het AGREE II-instrument (Appraisal of Guidelines for Research & Evaluation II), dat een internationaal breed geaccepteerd instrument is. [Brouwers 2010] Voor een stap-voor-stapbeschrijving hoe een evidence-based richtlijn tot stand komt, wordt verwezen naar het stappenplan Ontwikkeling van Medisch Specialistische Richtlijnen van het Kennisinstituut van Medisch Specialisten.

Juridische betekenis van richtlijnen

Richtlijnen zijn geen wettelijke voorschriften maar wetenschappelijk onderbouwde en breed gedragen inzichten en aanbevelingen waaraan zorgverleners zouden moeten voldoen om kwalitatief goede zorg te verlenen. Aangezien richtlijnen uitgaan van ‘gemiddelde patiënten’, kunnen zorgverleners in individuele gevallen zo nodig afwijken van de aanbevelingen in de richtlijn. Afwijken van richtlijnen is, als de situatie van de patiënt dat vereist, soms zelfs noodzakelijk. Een richtlijn beschrijft wat goede zorg is, ongeacht de financieringsbron (Zorgverzekeringswet (Zvw), Wet langdurige zorg (Wlz), Wet maatschappelijke ondersteuning (Wmo), aanvullende verzekering of eigen betaling door de cliënt/patiënt). Opname van een richtlijn in een register betekent dus niet noodzakelijkerwijs dat de in de richtlijn beschreven zorg verzekerde zorg is. Informatie over kosten zoals beschreven in de richtlijn is gebaseerd op beschikbare gegevens ten tijde van schrijven.

Knelpuntenanalyse

In de eerste vergadering zijn knelpunten en wensen ten aanzien van de richtlijn geïnventariseerd door de werkgroepleden. Tevens zijn er knelpunten aangedragen door NVVN, NHG, NVKG, NVK, NIP, NVH, V&VN, HPN, NIV en KNMP. Tevens werden uitgenodigd Zorgverzekeraars Nederland (ZN), Nederlandse Vereniging Ziekenhuizen (NVZ), Zorginstituut Nederland (ZiNL), Vereniging Innovatieve Geneesmiddelen (VIG) en de Nederlandse Federatie van Universitair Medische Centra (NFU).

Uitgangsvragen en uitkomstmaten

Op basis van de uitkomsten van de knelpuntenanalyse zijn door de werkgroep uitgangsvragen opgesteld. Per uitgangsvraag zijn klinisch relevante uitkomstmaten opgesteld, waarbij zowel naar gewenste als ongewenste effecten is gekeken. De werkgroep heeft deze uitkomstmaten gewaardeerd volgens hun relatieve klinisch belang bij de besluitvorming rondom aanbevelingen.

Strategie voor zoeken en selecteren van literatuur

Voor de afzonderlijke uitgangsvragen is aan de hand van specifieke zoektermen een systematische zoekstrategie uitgevoerd in (verschillende) elektronische databases Embase en MEDLINE. In eerste instantie is gezocht naar studies met de hoogste mate van bewijs. De aldus gevonden studies zijn door twee arts-onderzoekers (TB en EdB) onafhankelijk van

elkaar geselecteerd op basis van titel en abstract en vooraf opgestelde selectiecriteria. Bij discrepantie is een derde persoon gevraagd. De beoordeling en uiteindelijke selectie op basis van volledige tekst is gedaan door arts-onderzoeker(s) van de NVDV. De geselecteerde studies zijn gebruikt om de uitgangsvraag te beantwoorden. De zoekstrategie en de gehanteerde selectiecriteria zijn te vinden in bijlage 4.

Kwaliteitsbeoordeling individuele studies

De beoordeling van de kwaliteit van het wetenschappelijk bewijs/onderzoeksgegevens is in de richtlijn voor het grootste deel tot stand gekomen met de GRADE-methode.

Bij de GRADE-methode (Grading Recommendations Assessment, Development and Evaluation) worden individuele studies systematisch beoordeeld, op basis van op voorhand opgestelde methodologische kwaliteitscriteria om zo het risico op vertekende studieresultaten (risk of bias) te kunnen inschatten. Deze beoordelingen kunt u vinden in de Risk of Bias (RoB)-tabellen, deze zijn op te vragen via de NVDV. Hiervoor is gebruikgemaakt van de Cochrane risk of bias tool. [Higgins 2011]

Tabel 1 geeft een kort overzicht van de indeling van methodologische kwaliteit van individuele studies volgens GRADE. Een volledige uitleg over de GRADE-methode valt buiten het bestek van deze richtlijn, zie hiervoor het 'GRADE handbook'. [Schünemann 2013, www.gradeworkinggroup.com]

Tabel 1. Indeling van methodologische kwaliteit van individuele studies volgens GRADE

GRADE-systeem	
Type bewijs	- Gerandomiseerd onderzoek = hoog - Observationele studie = laag - Elk ander bewijs = zeer laag
Factoren die de kwaliteit van bewijs kunnen verlagen*	- Ernstige of zeer ernstige beperkingen in de kwaliteit van de studie - Indirectheid van het bewijs - Belangrijke inconsistentie tussen studies - Imprecisie - Grote kans op 'publicatiebias'
Factoren die de kwaltiteit van bewijs kunnen verhogen**	- Sterk bewijs voor een associatie – significant relatief risico van > 2 (< 0,5) gebaseerd op consistent bewijs uit twee of meer observationele studies, zonder plausibele 'confounders' (+1) - Zeer sterk bewijs voor een associatie – significant relatief risico van > 5 (< 0,2) gebaseerd op direct bewijs zonder belangrijke bedreigingen voor de validiteit (+2) - Bewijs voor een dosis respons gradiënt (+1) - Alle plausibele 'confounders' zonder het effect te hebben verminderd (+1)

* Elk criterium kan de kwaliteit verminderen met 1 stap of bij zeer ernstige beperkingen met 2 stappen.

** Verhogen kan alleen indien er geen beperkingen zijn t.a.v. de studiekwaliteit, imprecisie, inconsistentie, indirectheid en publicatiebias.

Samenvatten van de literatuur

De relevante onderzoeksgegevens van alle geselecteerde studies zijn overzichtelijk weergegeven als 'karakteristieken en resultaten van geïncludeerde studies'. De belangrijkste bevindingen uit de literatuur met betrekking op de vooraf opgestelde uitkomstmaten zijn beschreven in de samenvatting van de literatuur.

Beoordelen van de kracht van het wetenschappelijke bewijs middels GRADE

De kracht van het wetenschappelijke bewijs is bepaald volgens de GRADE-methode. (zie http://www.gradeworkinggroup.org/).

GRADE onderscheidt vier gradaties voor de kwaliteit van het wetenschappelijk bewijs: hoog, redelijk, laag en zeer laag (zie tabel 2). Deze gradaties verwijzen naar de mate van zekerheid die er bestaat over de literatuurconclusie. [Schünemann, 2013]

Tabel 2. Kwaliteit van bewijs van conclusies volgens GRADE

GRADE	Definitie
Hoog	– er is hoge zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt zoals vermeld in de literatuurconclusie; – het is zeer onwaarschijnlijk dat de literatuurconclusie verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Redelijk	– er is matige zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt zoals vermeld in de literatuurconclusie; – het is mogelijk dat de conclusie verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Laag	– er is lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt zoals vermeld in de literatuurconclusie; – er is een reële kans dat de conclusie verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Zeer laag	– er is zeer lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt zoals vermeld in de literatuurconclusie; – de literatuurconclusie is zeer onzeker.

Formuleren van conclusies

Voor elke relevante uitkomstmaat werd het wetenschappelijk bewijs samengevat in een of meerdere literatuurconclusies waarbij het niveau van bewijs werd bepaald volgens de GRADE-methode. De werkgroepleden maakten de balans op van elke interventie (overall conclusie). Bij het opmaken van de balans werden de gunstige en ongunstige effecten voor de patiënt afgewogen. De overall bewijskracht wordt bepaald door de laagste bewijskracht gevonden bij een van de kritieke uitkomstmaten. Bij complexe besluitvorming waarin naast de conclusies uit de systematische literatuuranalyse vele aanvullende argumenten (overwegingen) een rol spelen, werd afgezien van een overall conclusie. In dat geval werden de gunstige en ongunstige effecten van de interventies samen met alle aanvullende argumenten gewogen onder het kopje 'Overwegingen'.

Overwegingen (van bewijs naar aanbeveling)

Om te komen tot een aanbeveling zijn naast (de kwaliteit van) het wetenschappelijke bewijs ook andere aspecten belangrijk en meegewogen, zoals de expertise van de werkgroepleden, de waarden en voorkeuren van de patiënt (patient values and preferences), kosten, beschikbaarheid van voorzieningen en organisatorische zaken. Deze aspecten werden, voor zover geen onderdeel van de literatuursamenvatting, vermeld en beoordeeld (gewogen) onder het kopje ‘Overige overwegingen’.

Formuleren van aanbevelingen

De aanbevelingen geven antwoord op de uitgangsvraag en zijn voor zowel de GRADE- en EBRO-methodiek gebaseerd op het beschikbare wetenschappelijke bewijs, de belangrijkste overige overwegingen en een weging van de gunstige en ongunstige effecten van de relevante interventies. De kracht of het niveau van het wetenschappelijk bewijs en het gewicht dat door de werkgroep wordt toegekend aan de overwegingen, bepalen samen de sterkte van de aanbeveling.
Conform de GRADE-methodiek sluit een lage bewijskracht van conclusies in de systematische literatuuranalyse een sterke aanbeveling niet a priori uit, en zijn bij een hoge bewijskracht ook zwakke aanbevelingen mogelijk. De sterkte van de aanbeveling wordt altijd bepaald door weging van alle relevante argumenten tezamen.

Organisatie van zorg

In de knelpuntenanalyse en bij de ontwikkeling van de richtlijn is expliciet rekening gehouden met de organisatie van zorg: alle aspecten die randvoorwaardelijk zijn voor het verlenen van zorg (zoals coördinatie, communicatie, (financiële) middelen, menskracht en infrastructuur). Randvoorwaarden die relevant zijn voor het beantwoorden van een specifieke uitgangsvraag maken onderdeel uit van de overwegingen bij de bewuste uitgangsvraag.

Kennislacunes

Tijdens de ontwikkeling van deze richtlijn is systematisch gezocht naar onderzoek waarvan de resultaten bijdragen aan een antwoord op de uitgangsvragen. Bij elke uitgangsvraag is door de werkgroep nagegaan of er (aanvullend) wetenschappelijk onderzoek gewenst is om de uitgangsvraag te kunnen beantwoorden. Een overzicht van de onderwerpen waarvoor (aanvullend) wetenschappelijk van belang wordt geacht, is als aanbeveling beschreven (zie bijlage 8.

Commentaar- en autorisatiefase

De conceptrichtlijn is aan de betrokken (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd ter commentaar. De commentaren zijn verzameld in een commentaarformulier/tabel en besproken met de werkgroep. Naar aanleiding van de commentaren is de conceptrichtlijn aangepast en definitief vastgesteld door de werkgroep. De definitieve richtlijn is aan de betrokken (wetenschappelijke) verenigingen en (patiënt)organisaties voorgelegd ter autorisatie en door hen geautoriseerd dan wel geaccordeerd. Zie daarvoor paragraaf ‘Autorisatie’.

Autorisatie

De richtlijn is geautoriseerd door de NVDV, NHG, V&VN, NIP, NVKG, NVK, HPN, NVI en NVvAKI op 10-05-2022.

Literatuur

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Bijlage 2: Overzicht werkgroepen en betrokken partijen

Werkgroeplid	Affiliatie en vereniging
Dhr. Dr. H.B. Thio, dermatoloog, (voorzitter)	Erasmus MC, Rotterdam, NVDV
Dhr. Dr. D.M.W. Balak, dermatoloog	UMC Utrecht, NVDV
Dhr. Drs. Z. Çiftçi (secretaris) (vanaf februari 2020)	Bureau NVDV, Utrecht, NVDV
Dhr. Drs. T. Boere (secretaris) (tot februari 2020)	Bureau NVDV, Utrecht, NVDV
Mw. Dr. M.C. Bolling, dermatoloog	UMC Groningen, NVDV
Dhr. Dr. J.J.E. van Everdingen, dermatoloog n.p.	Directeur NVDV, Utrecht
Dhr. Dr. R.A. Faaij, klinisch geriater	Diakonessenhuis, Utrecht, NVKG
Dhr. Drs. P.M.J.H. Kemperman, dermatoloog	Amsterdam UMC & Dijklander ziekenhuis, Purmerend, NVDV
Mw. Drs. T.A. Kouwenhoven, dermatoloog i.o.	Radboudumc. Nijmegen, NVDV
Dhr. Drs. A.S.H.J. Lokin, AIOS dermatologie	Amsterdam UMC, NVDV
Mw. Drs. H. Heineman, huisarts	Groningen, NHG
Mw. L. Meerkerk, verpleegkundig specialist	Haaglanden MC, den Haag, V&VN
Mw. Drs. H. Rijk-van Gent, kinderarts	Antonius ziekenhuis, Sneek, NVK
Dhr. Dr. R. Rosken, internist-allergoloog-immunoloog	Zaans Medisch Centrum, NVvAKI
Mw. Dr. M.E. Schram, dermatoloog	ZBC Multicare, Hilversum, NVDV
Mw. Dr. S. Spillekom- van Koulil, psycholoog	Radboud UMC, Nijmegen, NIP
Mw. Drs. M. Stolting (secretaris) (vanaf september 2021)	Bureau NVDV, Utrecht, NVDV
Mw. E. Swanborn	Voorzitter HPN

Overzicht betrokken partijen chronische jeuk 2022*	Zitting neming in werkgroep	Knelpunten analyse	Commentaarfase	Autorisatie	Opmerkingen
Wetenschappelijke verenigingen					
Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV)	X	X	X	X	
Nederlandse vereniging Neurologie (NVN)	-	X	X	-	
Nederlandse Vereniging voor Klinische Geriatrie (NVKG)	X	X	X	X	
Nederlandse Internisten Vereniging (NIV)	X	X	X	X	
Overige organisaties					
Verpleegkundigen & Verzorgenden Nederland (V&VN)	X	X	X	X	
Nederlands Huisartsen Genootschap (NHG)	-	-	X		
Nederlandse Vereniging voor Kindergeneeskunde (NVK)	X	-	X	X	
Nederlandse Vereniging voor Allergologie en Klinische Immunologie (NVvAKI)	X	-	X	X	
Nederlands Instituut van Psychologen (NIP)	X	-	X	X	
Patiëntenverenigingen					
Huid Nederland (HN)	X		X		
Stakeholders					
Nederlandse Vereniging Ziekenhuizen (NVZ)			X		
Nederlandse Federatie van Universitair Medische Centra (NFU)			X		
Koninklijke Nederlandse maatschappij ter bevordering van de pharmacie (KNMP)		X	X		
Zorgverzekeraars Nederland (ZN)			X		
Zorginstituut Nederland (ZiN)		X			
Vereniging Innovatieve Geneesmiddelen (VIG)			X		
Nederlandse Vereniging voor Ziekenhuis Apothekers (NVZA)			X		

**alle partijen werden uitgenodigd voor de knelpuntenanalyse (invitational conference) en de commentaarfase. Deelname aan de werkgroep en autorisatie wordt enkel aan de wetenschappelijke verenigingen, patiëntenverenigingen en overige organisaties voorgelegd.*

Bijlage 3: Belangenverklaringen

De KNMG-Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden hebben schriftelijk verklaard of ze in de laatste drie jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatie management, kennisvalorisatie) hebben gehad. Een overzicht van de belangen van werkgroepleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van de Nederlandse Vereniging voor Dermatologie en Venereologie.

Werkgroeplid	Hoofdfunctie(s)	Nevenfunctie(s)	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Getekend op	Acties (voorstel)
Dhr. Dr. H.B. Thio, (voorzitter)	Dermatoloog Erasmus MC, Rotterdam	- Spreker/lid medische adviesraden en organisatie nascholingen dermatologen - Gesponsord door: Abbvie, Celgene, Janssen Pharmaceutica, Novartis, Almirall, UCB, Leopharma, Mylan	Geen	Geen	Geen	Geen	Geen	12-12-2019	Geen
Dhr. Dr. D.M.W. Balak	Dermatoloog, UMC Utrecht	- Spreker/voorzitter nascholingen dermatologen - Gesponsord door: Abbvie, Celgene, Janssen Pharmaceutica, Novartis, Leopharma, Lilly, Sanofi-Genzyme	Geen	Geen	Geen	Geen	Geen	11-12-2019	Geen
Mw. Dr. M.C. Bolling	Dermatoloog, UMC Groningen	Geen	- Stock Apreciation Rights, Philae Pharmaceuticals	Geen	Geen	Geen	Geen	04-12-2019	Geen
Dhr. Dr. R.A. Faaij,	Klinisch geriater, Diakonessenhuis, Utrecht	Geen	Geen	Geen	Geen	Geen	Geen	11-12-2019	Geen

Dhr. Drs. P.M.J.H. Kemperman	Dermatoloog, Amsterdam UMC & Dijklander ziekenhuis, Purmerend	- Bestuurslid Nederlandse Vereniging voor Psychodermatologie - Spreker lezingen Gesponsord door: Novartis, Sanofi, Leopharma, Galderma, Lilly	Geen	Geen	Geen	Geen	Geen	11-12-2019	Geen
Dhr. Drs. A.S.H.J. Lokin	Dermatoloog i.o. Amsterdam UMC	- Commissielid 'Patiëntenvoorlichting' Nederlandse Vereniging voor Dermatologie en Venereologie	Geen	Geen	Geen	Geen	Geen	08-12-2019	Geen
Mw. L. Meerkerk	Verpleegkundig specialist, Haaglanden MC, den Haag	Bestuurslid B3 Positive	Geen	Geen	Geen	Geen	Geen	27-11-2019	Geen
Mw. Drs. H. Rijk-van Gent	Kinderarts, Antonius ziekenhuis, Sneek	Geen	Geen	Geen	Geen	Geen	Geen	07-12-2019	Geen
Mw. Dr. M.E. Schram	Dermatoloog, ZBC Multicare, Hilversum	Spreker Hogeschool, huidtherapie	Geen	Geen	Geen	Geen	Geen	10-12-2019	Geen
Mw. Dr. S. Spillekom- van Koulil	Psycholoog, Radboud UMC, Nijmegen	- Bestuurslid Nederlandse Vereniging voor Psychodermatologie	Geen	Geen	Geen	Geen	Geen	03-12-2019	Geen
Mw. E. Swanborn	Voorzitter HPN	- Voorzitter Huidpatiënten Nederland - Voorzitter Stichting Lichen Sclerosus	Geen	Geen	Geen	Geen	Geen	11-12-2019	Geen

Bijlage 4: zoekstrategieën Chronische Jeuk

Inclusiecriteria	Exclusiecriteria
– Humane studies – Vanaf 2000 – Nederlands- en Engelstalige studies – Prospectieve studies, RCTs, systematische reviews en relevante observationele studies, niet-gerandomiseerde studies	– Dubbele publicaties – N < 10 – Interventie niet beschikbaar in NL – Full-tekst niet beschikbaar –

Uitgangsvragen

1 Wat is de etiologie van chronische jeuk?
2 Welke vorm van diagnostiek (anamnese, lichamelijk onderzoek, aanvullend onderzoek) moet minimaal verricht worden bij chronische jeuk die niet het gevolg is van een huidziekte?
3 Welke lokale therapie komt in aanmerking bij de behandeling van chronische jeuk en welke lokale behandeling heeft de voorkeur?
4 Welke systemische therapie komt in aanmerking bij de behandeling van chronische jeuk en welke systemische behandeling heeft de voorkeur?
5 Wat is de effectiviteit van psychosomatische therapie bij chronische jeuk?

Resultaten

Uitgangsvraag	MEDLINE	EMBASE	Totaal (na ontdubbelen)
Systemische therapie			
• Gabapentine	76	607	631
• Naltrexon	50	334	361
• Nortriptyline	1	143	143
• Antihistaminica	662	556	865
• Amitriptyline + Doxepine	31	442	432
Lokale therapie			
• UVB-therapie	266	1339	1529
Psychologische behandeling			
• Psychologische behandeling	41	417	439

Gabapentine

EMBASE (datum 17-12-2019)

No.	*Zoektermen*	*Resultaten*
#8	#6 AND #7	**607**
#7	'gabapentin'/exp OR '1 (aminomethyl) cyclohexaneacetic acid' OR 'ci 945' OR 'ci945' OR 'dineurin' OR 'gabalept' OR 'gabaliquid geriasan' OR 'gabapentin' OR 'gabatin' OR 'gantin' OR 'go 3450' OR 'go3450' OR 'goe 3450' OR 'goe3450' OR 'gralise' OR 'kaptin' OR 'keneil' OR 'neurontin' OR 'neurotonin' OR 'nupentin'	**30,274**
#6	#1 AND #5	**32,464**
#5	#2 OR #3 OR #4	**4,477,415**
#4	. AND 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**2,445,575**
#3	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2,322,426**
#2	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**467,005**
#1	('pruritus'/exp OR 'itch' OR 'itching' OR 'pruritis' OR 'pruritus') AND ('pruritus'/exp OR 'itch':ti,ab OR 'itching':ti,ab OR 'pruritis':ti,ab OR 'pruritus':ti,ab) AND ([dutch]/lim OR [english]/lim) AND [1999-2019]/py	**80,705**

MEDLINE (datum 18-12-2019)

Zoektermen

1 exp pruritus/ or exp pruritis/ or exp itch/ or exp itching/ (13459)
2 (pruritus or pruritis or itch or itching).ab,ti,kw. (26219)
3 1 or 2 (31662)
4 limit 3 to (yr="1999 -Current" and (dutch or english)) (19343)
5 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or l iterature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (425646)
6 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or

((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1931567)

7 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (3331949)

8 5 or 6 or 7 (4900886)

9 4 and 8 (8539)

10 exp gabapentin/ or exp gabatin/ or exp ci 945/ or exp dineurin/ or exp gabalept/ or exp gabaliquid geriasan/ or exp gantin/ or exp go 450/ or exp gralise/ or exp kaptin/ or exp keneil/ or exp neurontin/ or exp neurotonin/ or exp nupentin/ (3653)

11 (gabapentin or gabatin or dineurin or neurontin or gantin or gralise or gabalept or neurotonin or nupentin).ab,ti,kw. (6038)

12 10 or 11 (6678)

13 9 and 12 (76)

Alle resultaten

Database	**Datum**	**# hits**
EMBASE	17-12-2019	607
MEDLINE	18-10-2019	76
Totaal		683
Duplicates		52
Netto aantal		**631**

Naltrexon

EMBASE (datum 17-12-2019)

No.	*Zoektermen*	*Resultaten*
#8	#6 AND #7	**334**
#7	'naltrexone'/exp OR '17 (cyclopropylmethyl) 4, 5alpha epoxy 3, 14 dihydroxymorphinan 6 one' OR 'antaxon' OR 'antaxone' OR 'celupan' OR 'en 1639a' OR 'en1639a' OR 'nalerona' OR 'nalorex' OR 'naltrel' OR 'naltrexone' OR 'naltrexone hydrochloride' OR 'nemexin' OR 'nodict' OR 'nutrexon' OR 'phaltrexia' OR 're-via' OR 'regental' OR 'revez' OR 'revia' OR 'trexan' OR 'vivitrex' OR 'vivitrol'	**15,925**
#6	#1 AND #5	**32,464**
#5	#2 OR #3 OR #4	**4,477,415**
#4	'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**2,445,575**
#3	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2,322,426**

#2	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**467,005**
#1	('pruritus'/exp OR 'itch' OR 'itching' OR 'pruritis' OR 'pruritus') AND ('pruritus'/exp OR 'itch':ti,ab OR 'itching':ti,ab OR 'pruritis':ti,ab OR 'pruritus':ti,ab) AND ([dutch]/lim OR [english]/lim) AND [1999-2019]/py	**80,705**

MEDLINE (datum 18-12-2019)

1 exp pruritus/ or exp pruritis/ or exp itch/ or exp itching/ (13459)
2 (pruritus or pruritis or itch or itching).ab,ti,kw. (26219)
3 1 or 2 (31662)
4 limit 3 to (yr="1999 -Current" and (dutch or english)) (19343)
5 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or l iterature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (425646)
6 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1931567)
7 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (3331949)
8 5 or 6 or 7 (4900886)
9 4 and 8 (8539)
10. exp naltrexone/ or exp antaxon/ or exp antaxone/ or exp celupan/ or exp nalerona/ or exp nalorex/ or exp naltrel/ or exp nexemin/ or exp nodict/ or exp nutrexon/ or exp phaltrexia/ or exp regental/ or exp revez/ or exp revia/ or exp trexan/ or exp vivitrex/ or exp vivitrol/ (7730)
11. (naltrexone or nalerona or antaxon or celupan or nodict or regental or phaltrexia or revia or trexan or vivitrex).ab,ti,kw. (6769)
12. 10 or 11 (9879)
13. 9 and 12 (50)

Alle resultaten

Database	**Datum**	**# hits**
EMBASE	17-12-2019	334
MEDLINE	18-10-2019	50
Totaal		384
Duplicates		23
Netto aantal		**361**

Nortriptyline

EMBASE (datum 17-12-2019)

No.	*Zoektermen*	*Resultaten*
#8	#6 AND #7	**143**
#7	'nortriptyline'/exp OR '10, 11 dihydro 5 (3 methylaminopropylidene) 5h dibenzo [a, d] [1, 4] cycloheptene' OR '10, 11 dihydro n methyl 5h dibenzo [a, d] cycloheptene delta 5, gamma propylamine' OR '3 (10, 11 dihydro 5h dibenzo [a, d] cyclohepten 5 ylidene) n methylpropylamine' OR '3 (3 methylaminopropylidene) 1, 2:4, 5 dibenzocyclohepta 1, 4 diene' OR '5 (3 methylaminopropylidene) 10, 11 dihydro 5h dibenzo [a, d] cycloheptene' OR '5 (alpha methylaminopropylidene) dibenzo [a, d] [1, 4] cycloheptadiene' OR '5 (alpha methylaminopropylidene) dibenzo [a, d] cyclohepta [1, 4] diene' OR 'acetexa' OR 'allegron' OR 'altilev' OR 'ateben' OR 'atilev' OR 'avantyl' OR 'aventyl' OR 'aventyl hcl' OR 'aventyl hydrochloride' OR 'desitriptyline' OR 'desmethylamitriptyline' OR 'l 38489' OR 'martimil' OR 'noramitriptyline' OR 'noritren' OR 'norline' OR 'norpress' OR 'nortrilen' OR 'nortrilene' OR 'nortriptylin' OR 'nortriptylin lundbeck' OR 'nortriptyline' OR 'nortriptyline hydrochloride' OR 'nortrix' OR 'nortryptilin' OR 'nortryptiline' OR 'nortryptyline' OR 'nortyline' OR 'norventyl' OR 'ortrip' OR 'pamelor' OR 'paxtibi' OR 'psychostyl' OR 'sensaval' OR 'sensival' OR 'vividyl'	**15,016**
#6	#1 AND #5	**32,464**
#5	#2 OR #3 OR #4	**4,477,415**
#4	. AND 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**2,445,575**
#3	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2,322,426**
#2	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**467,005**
#1	('pruritus'/exp OR 'itch' OR 'itching' OR 'pruritis' OR 'pruritus') AND ('pruritus'/exp OR 'itch':ti,ab OR 'itching':ti,ab OR 'pruritis':ti,ab OR 'pruritus':ti,ab) AND ([dutch]/lim OR [english]/lim) AND [1999-2019]/py	**80,705**

MEDLINE (datum 18-12-2019)

1 exp pruritus/ or exp pruritis/ or exp itch/ or exp itching/ (13459)
2 (pruritus or pruritis or itch or itching).ab,ti,kw. (26219)
3 1 or 2 (31662)
4 limit 3 to (yr="1999 -Current" and (dutch or english)) (19343)

5 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or l iterature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (425646)
6 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1931567)
7 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (3331949)
8 5 or 6 or 7 (4900886)
9 4 and 8 (8539
10 exp nortriptyline/ or exp acetexa/ or exp allegron/ or exp altilev/ or exp ateben/ or exp atilev/ or exp avantyl/ or exp aventyl/ or exp aventyl hcl/ or exp aventyl hydrochloride/ or exp desitriptyline/ or exp desmethylamitriptyline/ or exp l 38489/ or exp martimil/ or exp noramitriptyline/ or exp noritren/ or exp norline/ or exp norpress/ or exp nortrilen/ or exp nortrilene/ or exp nortriptylin/ or exp nortriptylin lundbeck/ or exp nortriptyline/ or exp nortriptyline hydrochloride/ or exp nortrix/ or exp nortryptilin/ or exp nortryptiline/ or exp nortryptyline/ or exp nortyline/ or exp norventyl/ or exp ortrip/ or exp pamelor/ or exp paxtibi/ or exp psychostyl/ or exp sensaval/ or exp sensival/ or exp vividy/ (2140)
11 (nortriptyline or acetexa or allegron or altilev or ateben or atilev or avantyl or aventyl or aventyl hcl or aventyl hydrochloride or desitriptyline or desmethylamitriptyline or l 38489 or martimil or noramitriptyline or noritren or norline or norpress or nortrilen or nortrilene or nortriptylin or nortriptylin lundbeck or nortriptyline or nortriptyline hydrochloride or nortrix or nortryptilin or nortryptiline or nortryptyline or nortyline or norventyl or ortrip or pamelor or paxtibi or psychostyl or sensaval or sensival or vividy).ab,ti,kw. (2383)
12 10 or 11 (3122)
13 9 and 12 (1)

Alle resultaten

Database	**Datum**	**# hits**
EMBASE	17-12-2019	143
MEDLINE	18-10-2019	1
Totaal		144
Duplicates		1
Netto aantal		**143**

Amitriptyline en Doxepine

EMBASE (datum 17-2-2020)

No.	*Zoektermen*	*Resultaten*
#8	#6 AND #7	**422**

#7	'doxepin'/exp OR '11 (6h) (3 dimethylaminopropylidene) dibenz [b, e] oxepin' OR 'adapin' OR 'anten' OR 'aponal' OR 'co dox' OR 'curatin' OR 'deptran' OR 'desidox' OR 'doneurin' OR 'doxal' OR 'doxepin' OR 'doxepin hydrochloride' OR 'doxepine' OR 'doxepine hydrochloride' OR 'expan' OR 'gilex' OR 'mareen' OR 'n, n dimethyl 3 (dibenz [b, e] oxepin 11 (6h) ylidene) propylamine' OR 'n, n dimethyldibenz [b, e] oxepin delta 11 (6h), gamma propylamine' OR 'nsc 108160' OR 'p 3693a' OR 'prudoxin' OR 'quitaxon' OR 'silenor' OR 'sinequan' OR 'sinquan' OR 'sinquane' OR 'zonalon' OR 'zonalon cream' OR 'amitriptyline'/exp OR '10, 11 dihydro 5 (gamma dimethylaminopropylidene) 5h dibenzo [a, d] 1, 4 cycloheptene' OR '10, 11 dihydro n, n dimethyl 5h dibenzo [a, d] cycloheptene delta5, gamma propylamine' OR '3 (10, 11 dihydro 5h dibenzo [a, d] cycloheptene 5 ylidene) n, n dimethylpropylamine' OR '5 (3 dimethylaminopropylidene) 10, 11 dihydro 5h dibenzo [a, d] cycloheptene' OR '5 (3 dimethylaminopropylidene) dibenzo [a, d] [1, 4] cycloheptadiene' OR '5 (gamma dimethylaminopropylidene) 5h dibenzo [a, d] 10, 11 dihydrocycloheptene' OR 'adepress' OR 'adepril' OR 'ambivalon' OR 'amilit' OR 'amineurin' OR 'amiplin' OR 'amiprin' OR 'amirol' OR 'amirol 10 fc' OR 'amirol 25 fc' OR 'amitid' OR 'amitril' OR 'amitrip' OR 'amitriptylene' OR 'amitriptylene hydrochloride' OR 'amitriptylin' OR 'amitriptylin-ct' OR 'amitriptyline' OR 'amitriptyline hydrochloride' OR 'amitriptylinumhydrochloride' OR 'amitryptiline' OR 'amitryptiline hydrochloride' OR 'amitryptilline' OR 'amitryptine' OR 'amitryptyline' OR 'amyline' OR 'amytril' OR 'amytriptiline' OR 'amytriptyline' OR 'amytryptiline' OR 'amyzol' OR 'anapsique' OR 'anp 3548' OR 'antalin' OR 'antitriptyline' OR 'apo-amitriptyline' OR 'damilene' OR 'damylene' OR 'deprelio' OR 'domical' OR 'elatrol' OR 'elatrolet' OR 'elavil' OR 'enafon' OR 'endep' OR 'enovil' OR 'etafon' OR 'etafron' OR 'euplit' OR 'lantron' OR 'laroxal' OR 'laroxyl' OR 'lentizol' OR 'miketorin' OR 'mk 230' OR 'n 750' OR 'n, n dimethyl 3 (dibenzo [a.d] 1, 4 cycloheptadien 5 yliden) propylamine hydrochloride' OR 'novoprotect' OR 'ormal' OR 'pinsaun' OR 'proheptadien' OR 'qualitriptine' OR 'redomex' OR 'redomex diffucaps' OR 'ro 4 1575' OR 'sarboten retard 75' OR 'sarotard' OR 'saroten' OR 'saroten retard' OR 'sarotena' OR 'sarotex' OR 'sarotex retard' OR 'stelminal' OR 'sylvemid' OR 'syneudon' OR 'syneydon' OR 'teperin' OR 'terepin' OR 'trepiline' OR 'tridep' OR 'tripta' OR 'triptanol' OR 'triptizol' OR 'triptyl' OR 'triptyline' OR 'trynol' OR 'tryptanol' OR 'tryptizol' OR 'trytomer' OR 'uxen' OR 'vanatrip'	**44,824**
#6	#1 AND #5	**32,628**
#5	#2 OR #3 OR #4	**4,553,693**
#4	'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**2,497,219**
#3	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2,351,075**

#2	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**478,023**
#1	('pruritus'/exp OR 'itch' OR 'itching' OR 'pruritis' OR 'pruritus') AND ('pruritus'/exp OR 'itch':ti,ab OR 'itching':ti,ab OR 'pruritis':ti,ab OR 'pruritus':ti,ab) AND ([dutch]/lim OR [english]/lim) AND [1999-2019]/py	**81,180**

MEDLINE (datum 17-02-2020)

1 exp pruritus/ or exp pruritis/ or exp itch/ or exp itching/ (13562)
2 (pruritus or pruritis or itch or itching).ab,ti,kw. (26458)
3 1 or 2 (31931)
4 limit 3 to (yr="1999 -Current" and (dutch or english)) (19605)
5 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or l iterature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (432751)
6 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1949849)
7 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (3367625)
8 5 or 6 or 7 (4951539)
9 4 and 8 (8656)
10 exp doxepin/ or exp amitriptyline/ or exp sinequan/ or exp tryptizol/ (7210)
11 (doxepin or amitriptyline or sinequan or tryptizol).ab,ti,kw. (7640)
12 10 or 11 (10241)
13 9 and 12 (31)

Database	**Datum**	**# hits**
EMBASE	17-02-2020	442
MEDLINE	17-02-2020	31
Totaal		473
Duplicates		41
Netto aantal		**432**

Antihistaminica

EMBASE (datum 17-12-2019) – Brede search (uiteindelijk niet gebruikt)

No.	*Zoektermen*	*Resultaten*

#8	#6 AND #7	**3,395**
#7	'antihistaminic agent'/exp OR 'anti histamine' OR 'anti histaminic agent' OR 'antihistamine' OR 'antihistamine agent' OR 'antihistamine drug' OR 'antihistamines' OR 'antihistaminic' OR 'antihistaminic agent' OR 'antihistaminic drug' OR 'antihistaminic factor' OR 'antihistaminics' OR 'antihistaminicum' OR 'histamine antagonist' OR 'histamine antagonists' OR 'histamine blocker' OR 'histamine blocking agent' OR 'histamine receptor antagonist' OR 'histamine receptor blocker' OR 'histamine receptor blocking agent'	**253,411**
#6	#1 AND #5	**32,464**
#5	#2 OR #3 OR #4	**4,477,415**
#4	'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**2,445,575**
#3	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2,322,426**
#2	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**467,005**
#1	('pruritus'/exp OR 'itch' OR 'itching' OR 'pruritis' OR 'pruritus') AND ('pruritus'/exp OR 'itch':ti,ab OR 'itching':ti,ab OR 'pruritis':ti,ab OR 'pruritus':ti,ab) AND ([dutch]/lim OR [english]/lim) AND [1999-2019]/py	**80,705**

EMBASE (datum 17-12-2019) – Gerichte search

No.	*Zoektermen*	*Resultaten*
#8	#6 AND #7	**556**
#7	#1 AND #5	**9,849**
#6	'antihistaminic agent'/mj OR 'anti histamine':ti,ab OR 'anti histaminic agent':ti,ab OR 'antihistamine':ti,ab OR 'antihistamine agent':ti,ab OR 'antihistamine drug':ti,ab OR 'antihistamines':ti,ab OR 'antihistaminic':ti,ab OR 'antihistaminic agent':ti,ab OR 'antihistaminic drug':ti,ab OR 'antihistaminic factor':ti,ab OR 'antihistaminics':ti,ab OR 'antihistaminicum':ti,ab OR 'histamine antagonist':ti,ab OR 'histamine antagonists':ti,ab OR 'histamine blocker':ti,ab OR 'histamine blocking agent':ti,ab OR 'histamine receptor antagonist':ti,ab OR 'histamine receptor blocker':ti,ab OR 'histamine receptor blocking agent':ti,ab	**29,481**
#5	#2 OR #3 OR #4	**4,477,642**
#4	'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up	**2,444,817**

	NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	
#3	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2,323,841**
#2	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**467,239**
#1	('pruritus'/mj OR 'itch':ti,ab OR 'itching':ti,ab OR 'pruritis':ti,ab OR 'pruritus':ti,ab) AND ([dutch]/lim OR [english]/lim) AND [1999-2019]/py	**32,427**

MEDLINE (datum 18-12-2019)

1 exp pruritus/ or exp pruritis/ or exp itch/ or exp itching/ (13459)
2 (pruritus or pruritis or itch or itching).ab,ti,kw. (26219)
3 1 or 2 (31662)
4 limit 3 to (yr="1999 -Current" and (dutch or english)) (19343)
5 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or l iterature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (425646)
6 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1931567)
7 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (3331949)
8 5 or 6 or 7 (4900886)
9 4 and 8 (8539
10 exp antihistaminic agent/ or exp anti histamine exp/ or exp anti histaminic agent/ or exp antihistamine/ or exp antihistamine agent/ or exp antihistamine drug/ or exp antihistamines/ or exp antihistaminic/ or exp antihistaminic agent/ or exp antihistaminic drug/ or exp antihistaminic factor exp/ or antihistaminics.mp. or exp antihistaminicum/ or exp histamine antagonist/ or exp histamine antagonists/ or exp histamine blocker/ or exp histamine blocking agent/ or exp histamine receptor antagonist/ or exp histamine receptor blocker/ or exp histamine receptor blocking agent/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (61355)

11 (antihistaminic agent or anti histamine or anti histaminic agent or antihistamine or antihistamine agent or antihistamine drug or antihistamines or antihistaminic or antihistaminic agent or antihistaminic drug or antihistaminic factor or antihistaminics or antihistaminicum or histamine antagonist or histamine antagonists or histamine blocker or histamine blocking agent or histamine receptor antagonist or histamine receptor blocker or histamine receptor blocking agent).ab,ti,kw. (15929)
12 10 or 11 (66989)
13 9 and 12 (662)

Alle resultaten

Database	**Datum**	**# hits**
EMBASE	17-12-2019	556
MEDLINE	18-10-2019	662
Totaal		1218
Duplicates		353
Netto aantal		**865**

UVB therapie

EMBASE (01-07-2020)

No.	*Zoektermen*	*Resultaten*
#8	#6 AND #7	**1,339**
#7	#3 OR #4 OR #5	**4,700,008**
#6	#1 AND #2	**3,604**
#5	'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**2,599,485**
#4	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2,403,493**
#3	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**498,744**
#2	('itch'/exp OR 'itch' OR 'itching'/exp OR 'itching' OR 'pruritis'/exp OR 'pruritis' OR 'pruritus'/exp OR 'pruritus' OR 'itch':ti,ab OR 'itching':ti,ab OR 'pruritis':ti,ab OR 'pruritus':ti,ab) AND ([dutch]/lim OR [english]/lim) AND [1999-2020]/py	**84,324**
#1	'phototherapy'/exp OR 'light therapy' OR 'light therapy':ti,ab OR 'light therapy, solar' OR 'phototherapy' OR 'phototherapy':ti,ab OR 'ultraviolet b radiation'/exp OR 'ultraviolet b radiation' OR 'ultraviolet b radiation':ti,ab OR 'narrowband ultraviolet b phototherapy'/exp OR	**103,592**

	'narrowband ultraviolet b phototherapy' OR 'narrowband ultraviolet b phototherapy':ti,ab	

MEDLINE (01-07-2020)

---
1 exp phototherapy/ (43873)
2 (phototherapy or UVB therapy or UVB phototherapy or Ultraviolet B therapy or Ultraviolet B phototherapy).ab,ti,kw. (11238)
3 exp pruritus/ or exp pruritis/ or exp itch/ or exp itching/ (15252)
4 (pruritus or pruritis or itch or itching).ab,ti,kw. (39859)
5 1 or 2 (49101)
6 3 or 4 (45798)
7 limit 5 to (yr="1999 -Current" and (dutch or english)) [Limit not valid in CDSR,CCA,CLCMR,DARE,ACP Journal Club,CLEED; records were retained] (34442)
8 limit 6 to (yr="1999 -Current" and (dutch or english)) [Limit not valid in CDSR,CCA,CLCMR,DARE,ACP Journal Club,CLEED; records were retained] (27557)
9 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (486860)
10 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (3248245)
11 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (3847003)
12 9 or 10 or 11 (6398581)
13 7 and 8 (592)
14 12 and 13 (312)
15 remove duplicates from 14 (266)

Psychologische behandeling

EMBASE (01-07-2020)

No.	*Zoektermen*	*Resultaten*
#8	#5 AND #7	**417**
#7	#1 AND #6	**900**
#6	'psychotherapy'/exp OR 'psychotherapy' OR 'psychotherapy':ti,ab,kw OR 'psychological therapy':ti,ab,kw	**317,529**
#5	#2 OR #3 OR #4	**4,633,805**
#4	'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de	**2,552,353**

	OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	
#3	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2,381,074**
#2	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**488,822**
#1	('itch'/exp OR 'itch' OR 'itching'/exp OR 'itching' OR 'pruritis'/exp OR 'pruritis' OR 'pruritus'/exp OR 'pruritus' OR 'itch':ti,ab OR ‘itching':ti,ab OR ‘pruritis':ti,ab OR 'pruritus':ti,ab) AND ([dutch]/lim OR [english]/lim) AND [1999-2020]/py	**83,634**

MEDLINE (01-07-2020)

1 exp psychotherapy/ (211656)
2 (psychotherapy or psychological therapy).ab,ti,kw. (64287)
3 1 or 2 (245910)
4 exp pruritus/ or exp pruritis/ or exp itch/ or exp itching/ (15147)
5 (pruritus or pruritis or itch or itching).ab,ti,kw. (49379)
6 4 or 5 (55295)
7 limit 3 to (yr="1999 -Current" and (dutch or english)) (126688)
8 limit 6 to (yr="1999 -Current" and (dutch or english)) (35610)
9 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (482384)
10 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (3209775)
11 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (3798878)
12 9 or 10 or 11 (6318483)
13 7 and 8 (107)
14 12 and 13 (54)
15 remove duplicates from 14 (41)

Bijlage 5: Exclusietabellen

Hoofdstuk Systemische therapie – Antihistaminica

Exclusies na full tekst screenings

RCTs en vergelijkende studies

Artikel	Reden van exclusie
Chunharas 2002	Geen full tekst beschikbaar
Ajayi 2014	Onduidelijk of het om chronische jeuk gaat
Hur 2019	Maar twee verouderde studies geïncludeerd t.o.v. Cochrane review uit 2019
Sher 2012	Maar 1 studie geïncludeerd met orale antihistaminica (die studie is tevens geïncludeerd in de Cochrane review), wat deze studie irrelevant maakt.
Weisshaar 2004	Jeuk werd opgewekt middels iontophoresis
Young 2000	Publicatie is teruggetrokken door de auteurs, omdat de review verouderd is.
Van Zuuren 2014	Samenvatting van de Apfelbacher 2013 cochrane review

Observationele studies

Artikel	Reden van exclusie
Mathur 2010	Longitudinale studie, worden geen uitkomstmaten na behandeling met antihistaminica gerapporteerd
Imaizumi 2003	Observationele studie, waar voor deze indicatie veel RCT's beschikbaar zijn.
Katagiri 2006	Pruritus/contact eczeem opgewekt door toediening diphencyprone

Overige designs

Artikel	Reden van exclusie
Bell 2009	Review, geen eigen data
Crownover 2004	Review, geen eigen data
Navarini 2010	Onduidelijk of het chronische jeuk betreft
Rayner 2017	Internationale review over prevalentie/behandeling.
Richarson 2015	Review, geen eigen data
Herman 2003	Review, geen eigen data
Klein 1999	Review, geen eigen data. De studies dateren van vóór 1999.
Munday 2002	Interventie niet beschikbaar in Nederland

Hoofdstuk Systemische therapie – Gabapentine

Exclusies na full tekst screenings

RCTs en vergelijkende studies

Artikel	Reden van exclusie
Siemens 2014	Eerdere versie van de Cochrane review uit 2016 (Siemens 2016, Pharmacological interventions for pruritus in adult palliative care patients (Review)).
Xander 2013	Eerdere versie van de Cochrane review uit 2016.
Razeghi 2009	Studie is niet gerandomiseerd en niet geblindeerd.
Goutos 2010	Ook acute burn-puritus (<72 na incident gabapentine toegediend. Geen chronische jeuk.

Overige designs

Artikel	Reden van exclusie
Ahern 2012	Review, geen eigen data.
Bell 2009	Review, geen eigen data.
Berger 2013	Review (geen eigen data) & case report.
Boozalis 2018	Review, geen eigen data.
Cheikh Hassan 2015	Retrospectieve cohort studie, studie niet van toepassing aangezien er veel RCT's beschikbaar zijn.
Fostini 2013	Review, geen eigen data.
Lau 2016	Review, geen eigen data.
Rayner 2017	Internationale review over prevalentie/behandeling.
Vila 2008	Review, geen eigen data.
Madsen 2016	Geen full tekst beschikbaar, alleen abstract.
Alapapara 2014	Geen full tekst beschikbaar.
Mugabure 2017	Alleen Spaanse full tekst beschikbaar.
Siemens 2016	Alleen abstract beschikbaar (preliminary results Cochrane review).
Tol 2010	Onduidelijk of het om een (placebo) gecontroleerde studie gaat.
Kneib 2019	Ook acute burn-puritus (<72 na incident gabapentine toegediend. Geen chronische jeuk.

Hoofdstuk Systemische therapie – Naltrexon

Exclusies na full tekst screenings

RCTs en vergelijkende studies

Artikel	Reden van exclusie
Ajayi 2014	Onduidelijk of het om chronische jeuk gaat
Siemens 2014	Deze studie is later geüpdatet in een Cochrane review (Siemens 2016, Pharmacological interventions for pruritus in adult palliative care patients (Review))
Xander 2013	Eerdere versie van de Cochrane review uit 2016

Observationele studies

Artikel	Reden van exclusie
Hegade 2014	Geen full tekst
Frech 2011	N < 10 (n=3)
Metze 1999 (Effective Treatment of Pruritus with Naltrexone, an Orally Active Opiate Antagonist)	Pilot studie van een andere geïncludeerde studie (Metze 1999, Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases)
Mansour 2006	Deel van de geïncludeerde patiënten heeft geen chronische jeuk

Overige designs

Artikel	Reden van exclusie
Miller 2011	Geen full tekst
Tandon 2007	Geen full tekst
Ahern 2012	Review, geen eigen data
Bassari 2015	Review, geen eigen data
Bergasa 2004 (Pruritus in chronic liver disease: mechanisms and treatment)	Review, geen eigen data
Bergasa 2004 (Treatment of the pruritus of cholestasis)	Review, geen eigen data
Hegade 2019	Longitudinale studie waarin de prevalentie van jeuk met de behandeling wordt gerapporteerd. Uitkomstmaten van de behandeling zelf worden niet beschreven.
Jones 2005	Case report en review
Kremer 2014	Review, geen eigen data
Lonsdale 2003	Review, geen eigen data
Mettang 2010	Review, geen eigen data
Phan 2010	Review, geen eigen data

Hoofdstuk Systemische therapie – Tricyclische antidepressiva

Exclusies na full tekst screenings

RCTs en vergelijkende studies

Artikel	Reden van exclusie
Andrade 2020	Cochrane review voortgekomen uit 1 RCT naar effect serlopitant bij chronische pruritus, geen analyse TCA's uitgevoerd bij gebrek aan studies
Andrade 2018	Cochrane review voorstel van bovenstaande

Observationele studies

Artikel	Reden van exclusie

Borson 2002	Irrelevante uitkomstvraag en uitkomstmaten, niet gekeken naar pruritus

Overige designs

Artikel	Reden van exclusie
Ansari 2019	Review van behandelopties bij notalgia paresthetica; 1 case report met amitriptyline als interventie
Greaves 2005	Review, geen eigen data
Malekmakan 2018	Review, geen eigen data
Masuda 2013	Case series, geen uitkomstmaten
Mirzoyev 2013	Case series, topicaal toegepaste TCA's
Pongcharoen 2016	Review, geen eigen data
Schmid 2019	Review, geen eigen data
Shaw 2007	Review, geen eigen data
Shenefelt 2011	Review, geen eigen data
Simonsen 2017	Review, geen eigen data
Qureshi 2019	Review, geen eigen data

Bijlage 6: Tabellen karakteristieken geïncludeerde studies

Karakteristieken en resultaten van geïncludeerde studies Antihistaminica (2020)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Ahuja (2011) **Post-burn pruritus** **Cetirizine versus Gabapentin versus Combination**	Type of study: randomized clinical trial Country: India Source of funding: Not reported Inclusion criteria: Age 12-70 years, Percentage of burns >5% TBSA, Depth of burns: predominantly second degree burns, Wounds either in healing phase (>80% epithelialized) or have completely healed < 1 month back Exclusion criteria: < 12 years or > 70 years, Co-morbid conditions such as diabetes, skin diseases, renal diseases, pregnancy, lactating females etc. which could have independently contributed to itch, patients unwilling to participate in the trial, patients who had undergone >1% TBSA split skin grafting to mainting a 'pure' cohort, wounds that had healed >1 month ago and where other topical	N total at baseline (n analysed): Sixty adult patients in the post-burn healing phase(wounds healed less than one month back – in early remodelling phase) with complaints of itching were allocated, equally (20 each), to either of the three groups: Groups A, B and C by random stratification. The mean age of patients in group A was 26.75 years, in group B 28.65 years and in group C 29.1 years old The sex:ratio for group A was 12:08, for group B 10:10 and for group C 9:11. The %TBSA burns was 28 for A, 26 for B and 29 for C. The mean VAS score for A was 6.6, for B 6.3 and for C 6.5	Group A: cetirizine 10mg 1dd (VAS2-5), 2dd (VAS6-8), 3dd (VAS9-10) Group B: gabapentin 300mg 1dd (VAS2-5), 300mg 2dd (VAS6-8), 300mg 3dd (VAS9-10) Group C: combination of both drugs ; C 10mg 1dd + G 300mg 1dd (VAS2-5), C 10mg 2dd + 300mg 2dd (VAS6-8), 10mg 2dd + 300mg 3dd (VAS9-10)	Not applicable	Length of follow up: 4 weeks Loss to follow up: None	1) Pruritus Patients in all the groups reported improvement in the extent of itch by a decrease in mean VAS score from days 0 to 28. Patients in Group A showed 58% decrease, Group B showed 95% decrease and Group C showed 94% decrease in their mean VAS scores. Statistically, if Groups A and B are compared, the difference in decrease of mean VAS scores between days 0 and 28 in Group B is highly significant (p< 0.01). Groups B and C show no significant difference in decrease. Delta mean VAS Cetirizine: 6.6 to 2.7 (58%) Delta mean VAS Gaba: 6.3 to 0.3 (95%) Delta mean VAS Combi: 6.5 to 0.35 (94%)	

	measures had been employed for itch relief.					SD were not provided for any of these results. 2) Side effects All the patients in Group A and Group C reported increased somnolence but there was no reported side effect in patients in Group B. No other side effect was recorded for any patient in any group.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Kawashima (2003) **Pruritus due to AD** **Fexofenadine versus Placebo**	Type of study: randomized, multicentre, controlled, double-blinded clinical trial → all patients underwent a 1-week placebo lead-in period, followed by randomization to fexofenadine HCl 60mg 2dd or placebo 2dd for 1 week. All patients also received topical therapy with 0.1% hydrocortisone butyrate 2dd. Country: Japan Source of funding: Funding for the trial and its publication was provided by Aventis Parma, which	N total at baseline (n analysed): 575 patients were recruited, with 164 excluded for violation of the study protocol. 411 patients were randomized to receive either fexofenadine (201) or placebo (199). The mean pruritus scores in the subject-selection period were 4.7 ± 0.7 in the fexofenadine group and 4.8 ± 0.7 in the placebo group, with no	Fexofenadine HCl 60mg 2dd1 (after 1 week lead-in period with placebo)	Placebo 2dd1	Length of follow up: 2 weeks Loss to follow up: A total of 11 patients dropped out due to pretreatment noncompliance (2), use of contra-indicated drugs(5), no registration data (1) and changed in the administration of permitted concomitant topical agents (3).	1) Mean change in pruritic score from baseline scored by self-assessed pruritus severity using a 5-point scale. Fexofenadine HCl 60 mg twice daily significantly decreased the severity of pruritus from baseline compared with placebo (mean change in score -0.75 (unadjusted 95% CI -0.62, -0.88) vs. -0.5 (CI -0.38, -0.62), respectively; P = 0.0005.	

	is also the employer of 2 of the authors. <u>Inclusion criteria</u>: Age 16 or older, diagnosed with AD, self-assessed pruritus score between 4 and 7 for the last 3 days of the, written informed consent. <u>Exclusion criteria</u>: Usage of a topical steroid preparation other than the 0.1% hydrocortisone butyrate twice daily within the 1-week placebo lead-in period. Usage of antiallergic agents, antihistamines, nonsteroidal anti-inflammatory agents, γ-globulin preparations, anticholinergics, tranquillizers, hypnotics, antipsychotic drugs, cold remedies containing antihistamine agents, and any other antiallergic or antipruritic drugs in the 6 days preceding the day of enrolment. The use of steroids and immunosuppressive agents was not allowed for 2 weeks before and during the 3-day subject selection period. Sustained-release steroid depot preparations and astemizole were not allowed for 4 weeks before and during the 3-day subject-selection period. Patients were also excluded if their pruritus was only associated with the face and head; they had a history of contact dermatitis induced by a topical steroid; a history of complications including severe hepatic disorder, renal disorder, cardiopathy or blood disease; or a prolonged QTc interval. Other exclusion criteria included: noncompliance during the 3-day	significant difference in the distribution between the groups (P = 0.241).				2) Adverse events 48 in the fexofenadine group (23.2%) and 45 in the placebo group (22.1) (p = 0.8)	

	subject-selection period; a change in the method of use or the class of topical preparation in the 1-week placebo run-in period; skin infections induced by bacteria, fungi or viruses; a history of epileptic attacks or organic brain lesions; and a history of drug allergy to antihistamines and antiallergic agents. Patients receiving specific hyposensitization, immunomodulation or light therapy, those who had participated in other clinical studies in the past 3–6 months, those with a history of fexofenadine use, and pregnant or nursing women were also excluded.						

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Domagala 2017 **Pruritus in psoriasis** **Clemastine versus Levocetirizine versus Placebo**	Type of study: Double-blinded, randomized and placebo-controlled trial Country: Poland Source of funding: Not reported. Inclusion criteria: 18 yrs or older with plaque type psoriasis(diagnosed at least 3 months prior to enrolment) and concomitant pruritus Exclusion criteria:	N total at baseline (n analysed): 61 patients Age (mean ± SD): Clemastine group: 55.1 ± 14.2, range 19-76 years Levocetirizine group: 53.9 ± 13.9, range 32-80 Placebo group: 54.2 ± 17.3, range 25-86 Sex (male/female): 24/37 (39.3%/60.7%)	Clemastine 1mg 2dd1 for 6 days or Levocetirizine 5mg 1dd1 in the evening and 1 placebo in the morning for 6 days To ensure blindness of the study all tablets were put in the starch petal by the	Placebo 2dd1 for 6 days	Length of follow up: 7 days Loss to follow up: None of the patients were forced to drop out of the study.	1) VAS Patients were asked to assess pruritus intensity over the last 24 h according to the 10-point visual analogue scale (VAS). Mean itch intensity before treatment was 4.6 ±2.8 points according to the VAS scale. Mean intensity of pruritus according to the VAS before treatment was **5.6 ±2.7 points** in the **clemastine** group, **4.7 ±3.2 points** in the **levocetirizine** group	

	Non-plaque form of psoriasis (erythrodermic, guttate or pustular). NYHA III or NYHA IV heart failure, itch that could be induced by other dermatological or systemic diseases, receiving any medications which are known to cause pruritus or have an antipruritic effect. Women who were pregnant or breast-feeding as well as patients with contraindications to antihistamines were also excluded.	*All patients received the same routine treatment of psoriatic skin lesions (topical treatment with keratolytics followed by anthralin/dithranol and UVB 311 nm phototherapy)*	hospital pharmacist and were given to the patients by a physician not involved in the study assessments.			and **3.6 ±1.9 points** in the **placebo** group (p = 0.07). A statistically significant decrease in mean VAS scoring was observed in clemastine and levocetirizine groups (p < 0.001), but not in the placebo group. The greatest improvement of VAS was seen in the clemastine group by **2.6 ±3.1** points comparing to levocetirizine (by **2.0 ±2.9 points**, p = 0.56) and placebo (by **0.5 ±2.3 points**, p = 0.01) groups. The difference between levocetirizine and placebo subgroups was also significant (p = 0.03). 2) DLQI Mean DLQI values before treatment and on day 7 did not differ significantly between groups (p = 0.11 and p = 0.38, respectively). A statistically significant decrease in DLQI scoring was observed on day 7 when compared to the baseline values in all groups. The greatest improvement was seen in the clemastine group (9.7 ±5.6 points, p < 0.0001) followed by the levocetirizine group: 6.6 ±6.2 points (p < 0.0001) and the placebo group: 3.3 ±3.3 points (p < 0.001)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Kwa (2019) **Post-burn pruritus** **Clemastine vs Doxepin cream**	Type of study: Multicenter triple-blind randomized controlled trial Country: Netherlands Source of funding: The study was funded by the Dutch Burns Foundation. The foundation had no involvement in the collection, analysis and interpretation of data, writing of the report, or in the decision to submit the article for publication. Inclusion criteria: 18 years of age and older, treatment in one of the three Dutch burn centers, healed burns and experiencing itch with an intensity of 3 and higher as scored on a Visual Analogue Scale (VAS) at the time of enrolment Exclusion criteria: Subjects unable to give informed consent, or unable to understand and	N total at baseline (n analysed): 31 subjects were included; 13(9 analysed) allocated to treatment with doxepin cream and placebo tablets and 18(13 analysed) subjects allocated to treatment with oral antihistamine clemastine and placebo cream. There were no statistically significant differences between the groups with regard to sex, age, TBSA, body surface area (BSA) of the study area, and presence of itch postburn	Doxepin cream 4dd and placebo tablet 2dd	Placebo cream 4dd and clemastine tablet 1mg 2dd	Length of follow up: 12 weeks Loss to follow up: 5 in the doxepin group, 2 in the clemastine group	1) VAS The primary outcome was the change in itch intensity as measured by a VAS of 10 cm, with 0 indicating 'no itch' and 10 indicating 'worst itch imaginable'. The VAS was assessed once daily using a subject journal from day 1 to 14 (D1–D14) and once at week 6 (W6) and once at week 12 (W12). Doxepin group: D1: 5.26 ± 2.14 -> D14: 3.21 ± 2.84 Clemastine group: D1: 5.67 ± 2.85 -> D14: 3.50 ± 2.54 Both study groups experienced a significant decrease in itch intensity between D1-D14 (doxepin group n = 9, p = 0.021; clemastine group n = 12, p = 0.010) and between D1 and W12 (doxepin group n = 5, p = 0.043; clemastine group n = 13, p = 0.019). The doxepin group also showed a	

	fill in VAS scores and questionnaires, subjects with a cutaneous or systematic disease that causes itch, or with any disease or condition that was associated with adverse effects using doxepin cream or oral selective anti-histamine.					significant decrease between D1 and W6 (n = 7, p = 0.028), but the clemastine group did not (n = 11, p = 0.213).	
Marquez (2011) **Uremic pruritus** **Gabapentin versus Desloratadine**	Type of study: Prospective, non-randomized, cross-over clinical trial Country: Argentina Source of funding: Not reported Inclusion criteria: Subjects were adults 18 years or older on stable haemodialysis for at least three months. Exclusion criteria: We excluded patients with chronic skin diseases (allergic, parasitic, infectious), chronic liver disease, systemic malignancies and those receiving chronic opiate therapy or corticosteroids. The use of emollients or other coadyuvant treatment for pruritus was	N total at baseline (n analysed): Twenty-two patients were assigned to the interventions. Of these, three did not complete the study (Figure 1), leaving 19 subjects for analysis. Age 54 SD 18.	Subjects who qualified for the study were taken off any antipruritic agents for a one-week run-in period. After this run-in/washout period, subjects were assigned to receive orally either desloratadine 5 mg or gabapentin 300 mg three times a week, after a 1-week washout period, each patient crossed-over to the alternate regien for another three weeks.		Length of follow up: Total 7 weeks. Both therapies three weeks with one week wash out period between both treatments. Loss to follow up: 4 patients in the gabapentin group	1) Pruritus, VAS (10cm) Both gabapentin and desloratadine resulted in decreased VAS scores compared with baseline, but only desloratadine reached statistical significance. There were no statistically significant differences between the two agents when comparing the final VAS for each group (from 5.95 to 4.6 (gaba) versus from 5.89 to 3.4 (deslo), p = 0.16). Eleven of 19 patients (58%) experienced a relative decrease in VAS of least 50% while on desloratadine, whereas 5 of 19 (16%) had similar reductions while on gabapentin (p = 0.049, Fisher's exact test). 2) Side effects While receiving gabapentin, 9 of 19 subjects (47%) reported fatigue and somnolence, and 4 of these patients	

	not allowed during the study.					discontinued use of the drug due to excessive somnolence, all after the first dose. While receiving desloratadine, one subject discontinued treatment due to nervousness. No other adverse events were reported.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Legroux-Crespel (2004) **Uremic pruritus** **Naltrexone versus Loratadine**	Type of study: Multicenter randomized controlled trial Country: France Source of funding: No information provided. Inclusion criteria: Inclusion criteria were pruritus (from 1 month or more (the mean duration of pruritus was 40.05 months (from 1 to 300 months)) in patients with chronic renal failure, hemodialysis and age superior to 18 years. Exclusion criteria: Exclusion criteria were all other possible causes of pruritus, pregnancy, lactation, hypersensitivity to naltrexone	N total at baseline (n analysed): N= 52 patients. There was no significant difference between the two groups for sex, age, nephrological diagnosis, characteristics of dialysis, characteristics of pruritus (duration, intensity), other treatments or biological variables (especially urea, creatinine and phosphate). The mean score of pruritus on day 0 was 4.85.	Naltrexone (50 mg/day)	Loratadine (10 mg/day)	Length of follow up: 2 weeks Loss to follow up: Altogether 10 patients with naltrexone (4 for vertigo, 3 for nausea, 1 for malaise, 2 for cramps, 1 for sleeping disturbances and 1 for anorexia) and with loratadine (1 for vomiting, 1 for malaise, 1 without relation with loratadine) were withdrawn from the study	Evaluation of all studied criteria (pruritus, quality of sleep, adverse events, biological examinations) was made on days 0, 7 and 14. 1) Pruritus: The severity of pruritus and the sleep disturbance were measured by a visual analogue scale (VAS, 10 point scale) The mean score of pruritus on **day 0 was 4.85**. On day 7, the mean score of pruritus was **4.54 for patients with naltrexone** and **3.96 for patients with loratadine** But 7 patients had a dramatic regression of	

	or loratadine, dependency on opioids and severe liver insufficiency.					pruritus on day 7 and day 14 (>3 units: marked improvement) with naltrexone (4 on day 7 and 5 on day 14 because of 2 withdrawals 2) Side effects: - Naltrexone induced 30 adverse events in 15 patients - Loratadine induced 3 adverse events in 2 patients	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Nakhaee (2015) **Uremic pruritus** **Hydroxyzine vs Avena sativa (colloidal oatmeal) vs Vinegar (topical)**	Type of study: RCT, Comparative three-armed trial with cross-over design Country: Iran Source of funding: Not reported Inclusion criteria: All the patients who entered the study were on hemodialysis at least twice weekly and experienced uremic pruritus for at least 2 weeks. Exclusion criteria:	N total at baseline (n analysed): In total, there were 25 participants with uremic pruritus who were treated with hemodialysis in the study. Age (mean ± SD): 57.04 years ± 12.20 Sex (male/female): 17 (73.9%)/6 (26.1%)	Hydroxyzine 10mg 1dd1 Wash-out period of 72 hours between treatments	Vinegar solution (30 ml synthetic white vinegar 5% in 500 ml of water), 2dd Avena Sativa lotion, 2dd	Length of follow up: Treatment duration of 2 weeks before both moments of cross-over. No informationon follow-up was provided. Loss to follow up: 2 in the vinegar solution group (kidney transplantation)	1) Pruritus, VAS (10cm) The patients were asked to record the severity of their pruritus on a VAS. Hydroxyzine group: Before 5.21 ± 1.82, After 3.56 ± 2.52 P < 0.001 Avena group: Before 5.21 ± 1.69 After 4.10 ± 2.34 P = 0.01 Vinegar group: Before 5.19 ± 1.88 After 3.73 ± 2.41 P < 0.001	

	Unwillingness to participate in the study, treatment complications such as allergic reaction to vinegar or Avena sativa, and kidney transplantation were exclusion criteria						
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Shohrati (2007) **Pruritus due to sulfur mustard** **Doxepin vs Cetirizine vs Hydroxyzine**	Type of study: A randomized , double-blind clinical trial Country: Iran Source of funding: No mention of funding in this study Inclusion criteria: Male gender, being a chemical-exposed veteran, having established SM-resulted pruritus for longer than 6 months and being available for further evaluation Exclusion criteria: Itching resulted from systemic or non-chemical induced skin diseases and history of any anti-pruritic treatment 3 months prior to the onset of the study. Patients who developed drug complication and/or hypersensitivity reactions	N total at baseline (n analysed): 68-70 sulfur-mustard veterans(male) with pruritus (after documented skin exposure to SM) The average of patients was 44.3+-6.3 years old in the Cetirizine group, 42.3+-5.4 in the Doxepine group, and 41.1+-6.2 in the Hydroxyzine group (P = 0.756). The mean initial pruritic scores in Cetirizine, Doxepine, and Hydroxyzine group were 38.2+-4.8, 37.2+-4.9, and 37.3+-5.1, respectively (P = 0.854). The age and severity of pruritus were not different among groups at the beginning of the study.	Hydroxyzine 25mg 1x/d for 4wk Cetirizine 10mg 1x/d for 4 wk Doxepin 10mg 1x/d for 4 wk	Not applicable	Length of follow up: 8 weeks Loss to follow up: Unmentioned in study, the results however show a high probability	1. Pruritus: Scored by calculating a Pruritic score (maximum of 48 points) and then categorized patients into 3 groups based on itching severity. Mild (1-16 points), Moderate (17-32 points), Severe (33-48 points) Successful treatment defined as a decrease rate of more than 5 scores in the Pruritic score. No statistical significance was found after comparison of Cetirizine, Doxepine and Hydroxyzine final pruritic scores. 2. Complications (=Adverse effects); 14 patients complained of sedation in the Doxepin group, 6 in the Cetirizine group, 18 in the	

	during the study were also immediately excluded.					Hydroxyzine group (P=0.238). 2 patients in each of the groups showed dizziness (P= 0.974) A statistically significant association between drug-induced sedation and therapeutic efficacy of the drugs was found (P= 0.035). No further breakdown was given.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Wang (2013) **Cutaneous pruritus** **Olopatadine versus Cetirizine**	Type of study: Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial Country: China Source of funding: Not reported Inclusion criteria: Patients (18–65 years) with symptoms of systemic or regional	N total at baseline (n analysed): A total of 174 patients were randomized 85 (Olopatadine) vs 87 (cetirizine) to the two intervention groups.	Olopatadine 5mg 2dd1; *morning* – Olopatadine 5mg + placebo *evening* – Olopatadine 5mg + placebo	Cetirizine 10mg 1dd1; *morning* – Cetirizine 10mg + placebo *evening* – placebo + placebo	Length of follow up: 2 weeks with follow-up moments at day 7 and day 14. Loss to follow up: Two patients from the cetirizine group were excluded from the FAS, 1 because of invalid efficacy data and 1 because of	1) Pruritus, VAS (100mm) Baseline VAS (p=0.323): OH group; 67.4±13.8 Cetirizine group: 65.7±12.3 In the OH group, the mean patient-assessed VAS scores on day 7 (48.7 ± 19.2 mm) and day 14 (31.5 ± 23.9 mm) were both significantly lower than at baseline (67.4 ± 13.8 mm; p < 0.001). In the cetirizine group, the VAS scores on day 7 (45.8 ± 18.4 mm) and day 14 (28.0 ± 20.5 mm) were also significantly lower than at baseline (65.7 ± 12.3 mm; p < 0.001). However, there were no significant between-group differences in VAS scores at the baseline (p = 0.323), day 7 (p =	

	pruritus, and without primary skin lesions or internal diseases such as tumors. All patients had a symptom severity score ≥3 (where 0 = no itching and 6 = severe itching) Exclusion criteria: Gravid and/or lactating female patients, individuals with 'high-risk' occupations (i.e. drivers and machine operators), patients who had participated in another clinical trial in the previous 3 months and those with a history of allergy to the study medication were specifically excluded from the study. The use of sedatives or tranquillizers also excluded patients from entry.				using prohibited medications	0.246) or day 14 visits (p = 0.381). 2) Adverse events A total of 40 subjects (47.1%) in the OH group and 36 (41.4%) in the cetirizine group (p = 0.453) reported one or more adverse events during the study with lethargy being the most frequent reported adverse event.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Kircik (2013) **Pruritus in atopic**	Type of study: Randomized, double-blind, placebo controlled study Country:	N total at baseline (n analysed): A total of 40 participants were included to the two	Levocetirizine 5mg 1dd	Placebo 1dd	Length of follow up: 4 weeks. Loss to follow up:	1) VAS Levocetirizine group: Baseline – 7.8	

dermatitis **Levocetirizine vs placebo**	United States <u>Source of funding:</u> Derm Research, PLLC <u>Inclusion criteria</u>: Outpatient, male or female subjects of any race, at least 18 years of age. Female subjects of childbearing potential must have a negative urine pregnancy test result at Baseline and practice a reliable method of contraception throughout the study. Definitive diagnosis of atopic dermatitis as per Rajka-Hanifin criteria. Visual Analog Scale (VAS) pruritus score of 6 cm or more (moderate to severe itching) at baseline. Willing to refrain from other antihistamines and topical steroids and topical immunomodulators for the duration of the study. Able to understand and comply with the requirements of the study and sign Informed Consent/Health Insurance and Portability Accountability Act (HIPAA) Authorization forms. <u>Exclusion criteria</u>: Female subjects who are pregnant (positive urine pregnancy test), breast-feeding, or who are of childbearing potential and not practicing a reliable method of birth control. Requiring oral treatment for their atopic dermatitis apart from oral antihistamines. History of hypersensitivity or idiosyncratic reaction to any component of the test medication , or to cetirizine. Atopic Dermatitis triggered by an unavoidable irritant/allergen.	intervention groups (Levocetirizine N=20 and Placebo N=20)			Levocetirizine group: 1 loss-of-follow up, 1 withdrawal by subject, 1 not provided. Placebo group: 2 loss-of-follow up, 1 lack of efficacy, 1 withdrawal by subject	(6.5 – 8.5) Week 4 – 4.15 (2.4 – 6.9) Placebo group: Baseline – 7.5 (7.00 – 8.00) Week 4 – 6.4 (2.5 – 7.3) 2) DLQI Levocetirizine group: Baseline – 7.5 (4.00 – 14.00) Week 4 – 2.00 (1.00 – 5.00) Placebo group: Baseline – 8.0 (7.00 – 13.00) Week 4 – 4.0 (1.0 – 7.5) 3) Adverse events Levocetirizine group 5/20 Placebo group 4/20	

	Skin disease/disorder that might interfere with the diagnosis or evaluation of atopic dermatitis (e.g., erythroderma, skin infection on the affected area, etc.) Non-compliance with the proper wash-out periods for prohibited medications. Uncontrolled chronic disease such as diabetes The presence of renal disease with mild, moderate or severe renal impairment. Medical condition that, in the opinion of the Investigator, contraindicates the subject's participation in the clinical study. Clinically significant alcohol or drug abuse, in the opinion of the Investigator. History of poor cooperation, non-compliance with medical treatment, or unreliability. Participation in an investigational drug study within 30 days of the Baseline Visit.						

Karakteristieken en resultaten van geïncludeerde studies Gabapentine (2020)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Amirkhanlou (2006) **Uremic pruritus** **Gabapentin versus ketotifen**	Type of study: Double-blind randomized clinical trial Country: Iran Source of funding: Not reported	N total at baseline (n analysed): A total of 52 hemodialysis patients with uremic pruritus in two groups were treated with gabapentin and ketotifen. The mean age of patients in group G was 60.2±7.4 years, and in group K was 57.6±6.2 years, which was not statistically significant (P=0.127). In group G, 12 patients (46.2%) were males and 14 patients (53.8%) were females, and in	Gabapentin capsules (Iran Daroo Pharmaceutical Co., Tehran, Iran) 1 mg twice daily for 2 weeks	Ketotifen (Abidi Pharmaceutical Co., Tehran, Iran) 1 mg twice daily for 2 weeks.	Length of follow up: 2 weeks Loss to follow up: None	1) Pruritus Before and at the end of study, pruritus severity were determined based on Shiratori's severity scores (0= no itching, 1= minimal, 2= mild, 3= moderate and 4= severe itching).	

	Inclusion criteria: All patients undergoing hemodialysis were similar in frequency and method. Exclusion criteria: Patients suffering from itchy skin condition (nonuremic pruritus) were excluded	group K, 13 patients (50%) were males and 13 patients (50%) were females, which was not significantly different (P=0.098).				Clinical response to treatment was determined as follows: (1) Complete response (no itching or minimal itching after treatment), (2) Partial response (mild or moderate severity of itching after treatment) and (3) No response (severe pruritus after treatment). In group Gabapentin, 3 patients (11.5%) did not respond to treatment, 9 patients (34.6%) had a partial response and 14 patients (53.8%) had a complete response to treatment. In group K, 6 patients (23.1%) did not respond to treatment, 7 patients (26.9%) had a partial response and 13 patients (50.0%) had a complete response to treatment. Hence, there was no significant difference between two groups in terms of the response to treatment (P=0.481) 2) Side effects Assessment of the side effects in both treatment groups showed that in both groups, 4 patients (15.4%) experienced drowsiness and 1 patient (3.8%) had dizziness	

						after taking gabapentin and Ketotifen.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Gobo-Oliveira (2018) **Uremic pruritus** **Gabapentin versus dexchlorpheniramine** **Exclusie-reden; Middel niet beschikbaar in NL**	Type of study: randomized, controlled, double-blinded clinical trial → all patients were instructed to apply cold cream for 15 days (prerandomization phase or phase 1) prior to the treatment (randomization phase or phase 2). Those who still complained of pruritus after phase 1 were randomized into two groups Country: Brazil Source of funding: Funding for the trial and its publication was provided by FUNADERSP Inclusion criteria: Age >18, CKD stage V, on HD for at least three months, persistent skin pruritus and no use of topical and/or systemic antipruritic drugs for at	N total at baseline (n analysed): Pre-randomisation: 71 patients. 60 patients remained in the study. The randomised groups were homogenous regarding the clinical, laboratory, and demographic characteristics (table 1), as well as the dialysis characteristics (table 2), with adequate dialysis parameters. Age: 64 SD 15 (gaba) 59 SD 12 (dex)	300 mg oral gabapentin thrice weekly after HD Both groups were instructed to take one tablet every 12 hours from two bottles identified as "Home" and "Dialysis.	6 mg oral dexchlorpheniramine twice daily Both groups were instructed to take one tablet every 12 hours from two bottles identified as "Home" and "Dialysis.	Length of follow up: 21 days Loss to follow up: Both in the GABA as in the DEX group one dropout was noted due to adverse effects.	1) Pruritus (VAS, 10 point scale) Out of 71 patients, nine (12%) had complete resolution of pruritus and were not included in phase 2. After phase 2, median pruritus VAS scores were significantly reduced by 80% in both groups [5 (4–8) to 2 (0–3) in GABA group and 5 (3–7) to 1 (0 –2) in DEX group] ($P < 0.01$) with no differences between them ($P > 0.07$). 2) Side effects In the GABA group 11 (36.7%) patients experienced adverse drug events, and drowsiness was the most frequent (17%). In the DEX group, eight (26.6%) had side effects. Other reported adverse drug events included sleepiness, fatigue, dizziness, and headache. The risk of experiencing these side effects was higher with	

	least one week before the beginning of the study. Exclusion criteria: Chronic skin disease (allergic, parasitic, or infectious), internal malignancy and the use of opioids or corticosteroids.					gabapentin treatment, but the results were not significant (RR = 1.37, P = 0.4098 3) QoL (DLQI) Overall, the DLQI was reduced by 50%, from 2 (1-3) to 1 (0-1); from 2 (1-3) to 1 (0-1) in the GABA group and from 2 (1-4) to 0 (0- 1) in the DEX group.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Gunal (2004) **Uremic pruritus** **Gabapentin versus placebo** **No SD reported; only narrative description**	Type of study: double-blinded clinical trial Country: Turkey Source of funding: Not reported. Inclusion criteria: All patients had histories of pruritus of >8 weeks duration. Their pruritus was not relieved by antihistamines, nicergoline or moisturizers. None of the patients had concomitant dermatological, liver or metabolic diseases associated with pruritus. Any medication with presumed antipruritic effects was discontinued 1 week before the study.	N total at baseline (n analysed): We enrolled in the trial 25 adult patients on haemodialysis who were asked to daily record the severity of their pruritus on a visual analogue scale. Age (mean ± SD): 55 ± 11, range 32-77 years, Sex (male/female): 14/11	**Gabapentin 300mg** (Neurontin; Parke-Davis, Goedecke GmbH, Freiburg, Germany) or placebo was administered orally thrice weekly at the end of haemodialysis sessions	Gabapentin 300mg (Neurontin; Parke-Davis, Goedecke GmbH, Freiburg, Germany) or **placebo** was administered orally thrice weekly at the end of haemodialysis sessions	Length of follow up: 9 weeks (including a 1 week wash out period) Loss to follow up: None of the patients was forced to drop out of the study due to adverse effects from gabapentin.	1) Pruritus / VAS The patients were asked to record the severity of their pruritus on a visual analogue scale once a day. The scale consisted of a 10cm horizontal line marked from 0 (denoting no itch) to 10 (denoting worst possible imaginable itch). A reduction in scores of >50% was considered as the desired improvement in symptoms during treatment The mean pruritus score before the study was 8.4±0.94 (range: 7–10). After placebo administration, that score decreased to 7.6±2.6 (range: 2–10; P=0.098). The scores of	

	Exclusion criteria: No exclusion criteria mentioned					four patients decreased by >50% with placebo. After gabapentin administration, the mean score decreased significantly to 1.2±1.8 (range: 0–8; P=0.0001;). Only one patient's symptoms did not improve significantly with gabapentin. 2) Side effects Somnolence, dizziness and fatigue were the most common side effects of gabapentin noticed during the trial. These adverse effects were mild to moderate and commonly occurred after the first dose of the drug.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Nofal (2016) **Uremic pruritus** **Gabapentin versus placebo**	Type of study: Randomized-controlled single-blinded trial Country: Egypt Source of funding: Not reported. Inclusion criteria:	N total at baseline (n analysed): Total: 54 The gabapentin group included 23 male patients (85.2%) and four female patients (14.8%) with mean age 51.569.96 years (range: 29–65 years). The placebo group included 18 male patients (66.7%)	Twenty-seven patients received **gabapentin 100mg capsules thrice weekly after every HD** in titrated oral dose, starting with 100mg. In cases with no significant improvement, the dose was gradually titrated up to a maximum of 300mg after each HD session.	Twenty-seven patients received **placebo thrice weekly after each HD** session for one month. In order to prepare the placebo, we emptied gabapentin capsules and refilled them with starch.	Length of follow up: 4 weeks Loss to follow up: No dropouts	1) Pruritus Severity of pruritus was measured by visual analog scale (VAS) and 5-D pruritus scale: at the commencement of the study and before every HD session (thrice weekly) till the end of the study (one month) and one week after stoppage of treatment.	

	Fifty-four uremic patients undergoing HD with UP for at least three months and not relieved by traditional therapy were enrolled into the study. Any medications with antipruritic effects were discontinued one week before the study. Exclusion criteria: Patients with blood haemoglobin <7g/dl, hyperphosphatemia, hypercalcemia, history of systemic disorders causing pruritus other than renal failure and concomitant dermatological disorders associated with pruritus were excluded.	and nine female patients (33.3%) with mean age 52.1569.94 years (range: 25–69 years).	The doses of gabapentin ranged from 100mg to 300mg after each HD session. Most patients improved on 100mg (17 patients, 62.9%), five patients (18.5%) improved on 200mg, two patients (7.4%) improved on 300mg and three patients (11.1%) did not improve even on 300mg			Gabapentin group, 24 patients (88.9%) responded well to gabapentin (the scores decreased by>50%), (11 patients) 40.7% of them became totally free from pruritus at the end of the study (one month). In placebo group, only six patients (22.2%) responded well to placebo. A highly statistical difference was detected in favour of gabapentin group (p<0.001). 2) Side effects Eighteen patients (66.7%) have no side effects. Nine patients (33.3%) reported adverse effects: dizziness in five patients (18.5%), somnolence in three patients (11.1%), and fatigue in one patient (3.7%). These adverse effects were mild to moderate.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Naini (2007) **Uremic pruritus**	Type of study: Randomized double blind, placebo-controlled trial Country: Iran Source of funding:	N total at baseline (n analysed): A total of 34 patients with end-stage renal disease (ESRD) (16 males and 18 females; mean age:	Gabapentin 400 mg (PharmaScience, Montreal, Canada) The prescribed medications were administered twice weekly, after each	Placebo The prescribed medications were administered twice weekly, after each HD	Length of follow up: 4 weeks Loss to follow up: None of the patients was forced to	1) Pruritus, VAS (10cm) The severity of the pruritus was measured at the commencement of the study and after each HD session using a visual analogue scale.	

Gabapentin versus placebo	Not reported <u>Inclusion criteria</u>: The included subjects were on maintenance HD twice a week for at least three months. Pruritus for more than 8 weeks and unresponsive to antihistamines. <u>Exclusion criteria</u>: The exclusion criteria included anemia (hemoglobin < 7 g/dl), hyperparathyroidism (serum parathormone >300 pg/ml, normal range: 9-55 pg/ml) and/or serum phosphorus > 7mg/dl. In addition, patients with any evidence of skin disease other than uremic pruritus, as opined by an experienced dermatologist, were excluded from the study.	62 ± 10, range: 43-81 years) were enrolled	HD session for four weeks.	session for four weeks.	drop out of the study due to side effects of the treatment.	The mean pruritus score at baseline was 7.2 ± 2.3 (range: 3-10). After four weeks of treatment, the mean decrease in pruritus score in gabapentin and placebo groups was 6.7 ± 2.6 and 1.5 ± 1.8, respectively (p<0.001). 2) Side effects Somnolence, dizziness, and nausea were the most commonly reported side effects of gabapentin. The severity of adverse effects was mild to moderate, and usually subsided within 5-10 days from the first dose of gabapentin. Also, one patient in the gabapentin group complained of attacks of dizziness in the first week of treatment, which gradually subsided.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Solak (2012) **Uremic pruritus** **Gabapentin versus pregabalin**	<u>Type of study:</u> Open-label, prospective, randomized crossover study <u>Country:</u> Turkey <u>Source of funding:</u> Not reported	<u>N total at baseline (n analysed):</u> Patients were randomized into either gabapentin (25 patients) or pregabalin (25 patients) treatment arms using computer	Gabapentin was administered at a dose of 300 mg after each haemodialysis session (thrice weekly). After a 6 week treatment period, patients underwent a	Pregabalin at a dose of 75 mg per day. After a 6 week treatment period, patients underwent a 2 week washout. Then we	<u>Length of follow up</u>: Total: 14 weeks 6 weeks pregabalin, 2 weeks wash out period, 6 weeks gabapentin. <u>Loss to follow up:</u>	1) Pruritus, VAS (10cm) The patients were asked to record the severity of their pruritus on a VAS. Overall, 29 out of 40 patients (72.5%) had self reported pruritus symptoms at baseline	

Single-arm study → non-comparative, no GRADE	Inclusion criteria: Criteria for inclusion in the study were as follows: prior diagnosis of peripheral neuropathy or being on drug treatment for peripheral neuropathy for at least 3 months, minimum 40 mm pain score in the Short Form of McGill Pain Questionnaire, undergoing haemodialysis for at least 6 months, achievement of dialysis adequacy (Kt/V > 1.2), and age >18 years. Exclusion criteria: Exclusion criteria were as follows: the presence of hepatic, cardiopulmonary and uncontrolled psychiatric disease, pain syndromes other than peripheral neuropathy, specific dermatologic disease, which may cause pain and/or pruritus, abnormal blood counts (white blood cells < 2500/mm3 and platelet count < 10 ¥ 103/mm3), presence of active malignancy, untreated hypothyroidism and patients with extremity amputation.	generated random numbers. Forty (12 males, 28 females) out of 50 patients completed the study. Mean age was 58.2 1 13.7.	2 week washout. Then we performed a crossover and reversed treatment groups for another 6 week period.	performed a crossover and reversed treatment groups for another 6 week period.	Ten patients were dropped because of various reasons.	evaluation. Mean VAS score at baseline was 5.84 1 1.38 (range 4–9). There was no difference between gabapentin and pregabalin in terms of improvement in pruritus (difference in VAS score and percent of difference in parentheses after treatment: -4.41 1 1.78 (77.9%) for gabapentin and -4.43 1 2.1 (79.2%) for pregabalin, respectively, P = 0.844) (Table 2). 2) Side effects Various adverse events were observed with the use of gabapentin (27) and pregabalin (17). There was no significant difference with regards to the frequency of adverse events between gabapentin and pregabalin despite a trend of more frequent observations in gabapentin treatment.	
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Rossi (2019)	Type of study: In this randomized, double-blind, placebo-controlled trial	N total at baseline (n analysed):	Gabapentin 100 mg or gabapentin 300 mg were administered	Matching placebo, manufactured by the hospital	Length of follow up: 3 weeks	1) Pruritus, VAS (100 cm)	

Uremic pruritus **Gabapentin versus placebo** **No SD presented with results; narrative description in guideline**	of gabapentin in hemodialysis patients with UP, we sought to determine the efficacy of two fixed-dose, after-dialysis drug regimens versus placebo. <u>Country:</u> Italy <u>Source of funding:</u> This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. <u>Inclusion criteria:</u> Patients on thrice-weekly hemodialysis who met the following criteria were included: (1) age above 18 years; (2) history of itch for more than 6 weeks as per the definition of chronic itch by the International Forum for the Study of Itch [3]; (3) female subjects had to be willing to use adequate contraception; (4) a negative serum pregnancy test at initial screening of female subjects with childbearing potential. <u>Exclusion criteria:</u> Exclusion criteria were as follows: (1) history of itch preceding kidney failure; (2) dermatologic conditions causing pruritus (e.g., atopic	Twenty-five patients were enrolled. Patients' characteristics at baseline and differences between treatment groups are listed in Tables 1 and 2, respectively. Four patients were excluded as they refused taking the drug after randomization. Of the remaining 21, 5 were in the 300 mg arm, 8 in the 100 mg arm and 8 in the placebo arm	after each DS for 2 weeks * Two patients developed neurological impairment in the form of excessive sedation (lethargy) respectively at days 9 and 10 of treatment. The treatment allocation of these two patients was then unmasked for safety concerns: both of them were in the 300 mg arm. Enrolment in this arm was no longer continued. Blinding was maintained thereafter, the patients being randomized only to gabapentin 100 mg or placebo.	pharmacy (identical appearance, taste, size) was administered after each DS for two weeks.	<u>Loss to follow up:</u> Four patients were excluded as they refused taking the drug after randomization. Two patients developed neurological impairment.	VASS and a sleep disturbance questionnaire adapted were also administered after each DS during the 2 weeks of therapy and a week after therapy withdrawal Itch reduction, measured as a change in the absolute VASS from day 0 to day 14, was statistically significant in the 100 mg arm ($p = 0.0078$) but not in the 300 mg arm (presumably for the small number of patients that could be analysed after enrolment in the latter arm was stopped) or in the placebo arm (Fig. 1a). No significant increase in VASS between day 14 and day 21 was observed in the three groups. A significant difference was observed in percent VASS reduction (day 14 vs. baseline) between the 100 mg and placebo, the 300 mg and placebo, the 300 mg and 100 mg arms (Fig. 1b). 2) Side effects With respect to treatment-related toxicity, no adverse reactions were observed other than those reported above in the	

	dermatitis, allergy); (3) hypereosinophilia (eosinophil count > 500/mm3) and/or serum IgE elevation (> 120 UI/mL); (4) elevated calcium–phosphorus product (> 60 mg2/dL2); (5) elevated serum biliary acids (> 6 µmol/L); (6) Kt/V < 1 (calculated with the equivalent renal clearance method) [4]; (7) treatment with glucocorticoids, opioids, anti-histamines and other potentially interfering therapy (e.g., ultraviolet therapy); (8) hypersensitivity to any of the components of the study drug; (9) active alcohol or drug abuse or history of such abuses in the preceding 6 months; (10) any of the following comorbidities: cholestasis, neoplasia, rheumatic diseases.					300 mg arm (See interventions).	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Marquez (2011) **Uremic pruritus**	Type of study: Prospective, non-randomized study Country: Argentina	N total at baseline (n analysed): Twenty-two patients were assigned to the interventions. Of these, three did not	Subjects who qualified for the study were taken off any antipruritic agents for a one-week run-in period. After this run-in/washout period,	Desloratadine 5 mg three times a week	Length of follow up: Total 7 weeks. Both therapies three weeks with one week wash out period	1) Pruritus, VAS (10cm) Both gabapentin and desloratadine resulted in decreased VAS scores compared with baseline, but only desloratadine reached	

Gabapentin versus Desloratadine	Source of funding: Not reported Inclusion criteria: Subjects were adults 18 years or older on stable haemodialysis for at least three months. Exclusion criteria: We excluded patients with chronic skin diseases (allergic, parasitic, infectious), chronic liver disease, systemic malignancies and those receiving chronic opiate therapy or corticosteroids. The use of emollients or other coadyuvant treatment for pruritus was not allowed during the study.	complete the study (Figure 1), leaving 19 subjects for analysis. Age 54 SD 18.	subjects were assigned to receive orally either desloratadine 5 mg or gabapentin 300 mg three times a week.		between both treatments. Loss to follow up: 4 patients in the gabapentin group	statistical significance. There were no statistically significant differences between the two agents when comparing the final VAS for each group (from 5.95 to 4.6 (gaba) versus from 5.89 to 3.4 (deslo), p = 0.16). Eleven of 19 patients (58%) experienced a relative decrease in VAS of least 50% while on desloratadine, whereas 5 of 19 (16%) had similar reductions while on gabapentin (p = 0.049, Fisher's exact test). 2) Side effects While receiving gabapentin, 9 of 19 subjects (47%) reported fatigue and somnolence, and 4 of these patients discontinued use of the drug due to excessive somnolence, all after the first dose. While receiving desloratadine, one subject discontinued treatment due to nervousness. No other adverse events were reported.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Bergasa (2006)	Type of study: Double-blind, randomized, placebo-controlled trial Country:	N total at baseline (n analysed): The study group consisted of 16 women whose	Gabapentin was obtained from the manufacturer and packaged at the research pharmacy in	Placebo	Length of follow up: 4 weeks Loss to follow up:	1) Pruritus, VAS (10cm) The perception of pruritus was assessed every hour while the	

Cholestatic pruritus **Gabapentin versus placebo** **Only narrative description**	USA <u>Source of funding:</u> Not reported <u>Inclusion criteria</u>: The trial was designed to study patients aged 18-80 years with chronic pruritus secondary to liver disease. <u>Exclusion criteria</u>: The exclusion criteria were history of hepatic encephalopathy, ascites, history of variceal bleeding, malignancy, inability to practice contraception, pregnancy, creatinine greater than 1.7 mg/dL, hemoglobin less than 10 g/dL, status of post–liver transplantation, and infection with the human immunodeficiency virus	median age was 49 years (range 44-63 years). Nine patients had primary biliary cirrhosis (PBC),one patient had primary sclerosing cholangitis (PSC), and 6 patients had chronic liver disease secondary to infection with the hepatitis C virus. The duration of the prurituswas1-12 years.	100- and 300-mg maroon capsules, like those of the placebo. Under code, the study drug was started at 100 mg by mouth 3 times a day for 3 days, to be increased, if necessary and in the absence of side effects, by 300 mg every 3 days to a maximum of 2,400 mg daily in divided doses.		Three of the 16 patients dropped out of the study— one (prior to randomization because she did not wish to remain hospitalized for baseline evaluation, one on day 2 because of side effects, and one ,who had been randomized to placebo, because of persistent severe pruritus within 2 weeks of randomization.	patients were awake with a 10cm visual analog scale. The mean VAS decreased significantly among those taking the placebo and in some patients on gabapentin (see table 1 paper). In conclusion, gabapentin did not provide a significant therapeutic advantage over the placebo; in fact, it was associated with an increase in the perception of pruritus and in HAS in some patients. Standard deviation or mean VAS change not reported. 2) Side effects On gabapentin, patient 2 experienced fatigue, patient 4 dizziness, patient 7 worsening symptoms of carpal tunnel syndrome, patient 8 vomiting, and patient 16 dizziness on increasing dose and a fluctuating rise in serum creatinine. Gabapentin was discontinued in these patients.	

						On placebo, patient 3 developed fatigue and leukopenia, and patient 7 developed symptoms of carpal tunnel syndrome.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Ahuja (2010) **Post burn pruritus** **Gabapentin versus cetirizine versus Gabapentin + cetirizine** **No SD's reported with the results; Narrative description in guideline**	Type of study: Randomized controlled trial Country: India Source of funding: Not reported Inclusion criteria: (a) Age: 12–70 years. (b) Percentage of burns: >5% total body surface area. (c) Depth of burns: predominantly second degree burns. (d) Wounds either in healing phase (>80% wounds have epithelialized) or have healed completely less than 1 month back Exclusion criteria: (a)	N total at baseline (n analysed): The study included 60 patients; 20 in each group. There was no significant difference in all the three groups with respect to mean age, sex distribution, mean percentage of TBSA burn and mean VAS score on day 0.	Gabapentin was administered according to VAS score; given in doses 300 mg/day, 300 mg twice daily and 300 mg thrice daily for VAS score 2–5, 6–8 and 9–10, respectively	Cetirizine was given in the dose of 10 mg/day if the VAS score was 2–5 and 10 mg, twice a day, if VAS score was ≥6. Combination therapy: VAS 2-5: C 10 mg OD + G 300 mg OD VAS 6-8: C 10 mg BD + G 300 mg BD VAS 9-10: C 10 mg BD + G 300 mg TID	Length of follow up: 4 weeks Loss to follow up: None	1) Pruritus, VAS (10cm) Assessment for itching with Visual Analog Scale (VAS) was done on days 0, 3, 7, 14, 21 and 28. The initial mean VAS score reduced 95% in gabapentin group compared to 52% for the cetirizine group, which was highly significant ($p < 0.01$). There was a 94% reduction in mean VAS score in the combination group which was comparable to the relief observed with gabapentin alone ($p > 0.05$). Delta mean VAS Cetirizine: 6.6 to 2.7 (54%) Delta mean VAS Gaba: 6.3 to 0.3 (95%) Delta mean VAS Combi: 6.5 to 0.35 (94%) 2) Side effects	

	Patients under 12 and more than 70 years of age (as assessments would have been difficult by visual analog scale in children and very elderly). (b) Patients with co-morbid conditions viz., diabetes, skin diseases, renal diseases, pregnancy, lactating females etc. which could have independently contributed to itch. (c) Patients not willing to be part of the trial. (d) Patients who had undergone >1% TBSA split skin grafting were excluded to maintain a 'pure' cohort. (e) Wounds that had healed more than a month ago and where other topical measures had been employed for relieving itch.					All the patients in Group Gaba and Group Combination reported increased somnolence but there was no reported side effect in patients in Group Cetirizine. No other side effect was recorded for any patient in any group.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments

Zachariah (2011) **Post burn pruritus** **Gabapentin (single-arm study)** **Narrative description in guideline**	Type of study: Prospective study with gabapentin Country: India Source of funding: Not reported Inclusion criteria: Our study subjects were patients with post-burn hypertrophic scars from 6 weeks to 2 years after the burn event complaining of pruritus, with failure of response to the standard first-line choice of antihistamines. All patients were initially given cetirizine tablet 10 mg twice daily for a week along with emollients, as per the existing guidelines. All patients not relieved of itching with cetirizine were offered gabapentin. Emollients were continued. Age group between 4 and 60 year Exclusion criteria: Exclusion criteria were patients outside this time period and the age limit, pregnant and lactating mothers, and subjects with known hepatic or renal impairment and known history of behavioural or psychological problems.	N total at baseline (n analysed): Twenty-three patients were included in the study, all having hypertrophic burn scars with complaint of pruritus not relieved with trial of antihistamines. Of the 23 patients, 10 were adult males, 9 females and 4 children.	Adult patients were started with 100 mg of gabapentin twice daily and gradually increased to 200– 300mg thrice daily depending on the dose response to itching and drug tolerance. The maximum dose administered in our adult subjects was 900 mg/day. Paediatric patients were started with 5 mg/kg, b.d., and the dose increased as required. The maximum dose required was 5 mg/kg, t.d.s.	None	Length of follow up: Patients continued the treatment for 6 months to 1 year depending upon the severity of their itch. Loss to follow up: There was no serious adverse effect which necessitated a drug withdrawal or dose reduction	1) Pruritus, 'Itch Severity Scale' Eighty-seven per cent of the patients (20/23) showed dramatic relief of itching within 1 month of starting the treatment. The mean pretreatment GABA score was 13.35 and the mean posttreatment GABA score at the end of the first month was 8.3625, with the change in mean score being −4.99. 2) Side effects The most commonly seen side effect in our study group was sedation, to which patients developed tolerance in the course of 1–2 weeks. This did not incapacitate the patients' activities of daily living in any way. Minor side effects like headache, dizziness and nausea were reported in a couple of patients initially, which subsided with dose adjustment or the addition of symptomatic drugs like acetaminophen and domperidone.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Kaul (2018) **Post-burn pruritus** **Gabapentin (+pregabalin)** **Narrative description in guideline – geen eigen data, geen comparison, jeuk gradatie ongevalideerd (patient reported improvement)**	Type of study: *Retrospective review* Country: USA Source of funding: Not reported Inclusion criteria: Patients who have been given gabapentin and/or pregabalin in outpatient setting for pruritus and neuropathic pain associated with major burn injury between May 2011 to August 2015 were identified by the pharmacy at Shriners Hospitals for Children. These patients had previously failed therapy with diphenhydramine and hydroxyzine. If gabapentin failed to alleviate the symptoms, then pregabalin was added. Exclusion criteria: Exclusion criteria were those that did not receive gabapentin and/or pregabalin, those without complaints of pruritus and those older than age 21.	N total at baseline (n analysed): Finally, 136 individual burn survivors receiving gabapentin, pregabalin, or both, were included in the study.	Gabapentin (+ pregabalin) The average effective dose of gabapentin was 23.9 ± 10.3 mg/kg/day for children ≤5 years, 27.0 ± 15.3 mg/kg/day for children 6–12 years, and 34.1 ± 15.7 mg/kg/day for children >12 years. The average effective dose of pregabalin was 6.5 ± 3.5 mg/kg/day for children 6–12 years and 4.7 ± 1.6 mg/kg/day for children >12 years.	None	Length of follow up: Retrospective study Loss to follow up: Retrospective study.	1) Pruritus, Itch Assessment Scale For individuals treated with only gabapentin, 91.4% had an adequate response for pruritus. 100% of individuals treated with both gabapentin and pregabalin had an adequate response for pruritus 2) Side effects Gabapentin was associated with hyperactivity in two individuals, and sedation in one individual. One individual reported nausea, vomiting, and headaches when taking both medications; this resolved when gabapentin was discontinued. One individual reported sedation while taking both medications.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Maciel (2014) **Notalgia paresthetica** **Gabapentin versus topical capsaicin** ***Care; allocation bias ? groups unevenly distributed***	Type of study: An experimental, non-randomized, parallel, non-blinded study Country: Brazil Source of funding: Not reported Inclusion criteria: 20 patients aged from 20 to 60 years old and with clinical and histopathological diagnosis of NP treated at the dermatology outpatient clinic. Exclusion criteria: Patients presenting with renal dysfunction or contraindications to the use of gabapentin were excluded from the study.	N total at baseline (n analysed): Of the 20 patients analyzed in this study, 12 had already received previous and short treatment with capsaicin soon after disease diagnosis, but nine of them interrupted the treatment at the beginning due to intense burning.	Group A (VAS > 5) comprised 10 patients who underwent treatment with gabapentin at a dose of 300 mg/day for four weeks.	Group B (VAS < 5) also comprised 10 individuals, but they underwent the standard topical treatment with daily doses of capsaicin 0.025% for four weeks	Length of follow up: 4 weeks Loss to follow up: None	1) Pruritus, VAS score (10 cm) After four weeks of treatment, patients answered again the VAS for calculating the degree of itching intensity and assessing their treatment response. A significant improvement in itching was observed in patients from **group A,** which was demonstrated by the decrease in mean VAS scores for itching. Before the treatment with gabapentin, mean VAS score was 9.5, and after treatment it decreased to 5.0, with a standard deviation of nearly ± 3.3 (Table 1). The p-value obtained (p≈0.002) allowed to conclude that there was a statistically significant difference In addition, nine patient from this group reported an improvement in itching severity, and none of the patients showed a higher score for itching after treatment, and only one patient maintained the same score after medication A discrete improvement in itching severity was observed in **group B**, but it was less significant than that observed in the group treatment with gabapentin. Mean VAS initial score of the patients from this group was 3.00 and final score was 2.00, with standard deviation of ± 2.3.	

						Six patients from this group did not report any change in itching severity even after topical administration of capsaicin; three patients reported an improvement in itching intensity, and one patient reported a worsening in the severity of itching symptoms. 2) QoL, DLQI The 20 participants of the study also answered a questionnaire that evaluated the Dermatology Life Quality Index (DLQI). Seventy-five percent of patients were classified as having mild-to-moderate impairment in QL, and 10% of patients obtained scores that revealed severe impairment 3) Side effects **Group A**: All patients from this group reported mild gastric discomfort and only one patient reported dizziness. **Group B:** All patients from this group reported intense burning as a treatment effect. There was no significant difference in group B (0.3125<p<0.4375).	

Karakteristieken en resultaten van geïncludeerde studies Naltrexon (2020)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments

Peer (1996) **Uremic pruritus** **Naltrexone versus placebo**	Type of study: Randomized double-blind placebo-controlled crossover study Country: Israel Source of funding: The study was supported by Travenol Laboratories, Israel. Naltrexone was given by Du Pont Pharmaceutical, USA Inclusion criteria: Persistent uremic pruritus, resistant to treatments such as antihistamines, intravenous lignocaine, antipruritic lotions, ultraviolet therapy, ketotifen, and cholestyramine Exclusion criteria: Non-uremic causes of pruritus, not well dialyzed, hyperparathyroidism,	N total at baseline (n analysed): 15 patients on hemodialysis with severe generalized pruritus	Naltrexone 50mg 1x/d for 1wk After 1 week crossover to placebo with 7 days washout between treatments	Placebo 1x/d for 1wk After 1 week crossover to Naltrexone with 7 days washout between treatments	Length of follow up: 3 weeks Loss to follow up: None	1) Pruritus: median VAS at baseline and post for each crossover cohort (pruritus scored every 6 hours on 10cm VAS) BL: 9.9 (IQR 9·85–9·95) Post:2.1 (IQR 1·5–2·15) for naltrexone-placebo sequence BL: 9.9 ((IQR 9·3–10·0) Post: 1·0 (IQR 0·4–1·15) for placebo-naltrexone sequence Treatment in favor of naltrexone 2) Side effect: heart-burn in two (13.3 %) patients and upper abdominal discomfort in three (20%) patients. During naltrexone treatment. No drop outs.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Pauli-Magnus (2000)	Type of study: A randomized placebo-controlled, double-blind crossover study Country: Germany	N total at baseline (n analysed): 23 patients with end-stage renal disease	Naltrexone 50mg 1x /d for 4wk After 1 week crossover to placebo with 7	Placebo 1x /d for 4wk After 1 week crossover to Naltrexone with 7 days washout	Length of follow up: 9 weeks. Loss to follow up: 7 patients. 4 due to gastrointestinal side effect (three during naltrexone treatment and one during placebo period)	1) Pruritus: VAS (10 point scale), patients were evaluated at the beginning of the study and at the end of weeks 1, 2, and 4 of each study period	

Uremic pruritus **Naltrexone versus placebo**	Source of funding: This study was supported by the Robert Bosch Foundation and the Khalil Foundation. Inclusion criteria: Male or female patients ranging in age from 20 to 85 with end-stage renal disease (ESRD) undergoing HD or PD treatment and who had substantial pruritus (not responding to antipruritic lotions, antihistamines, ultraviolet therapy, oral activated charcoal, and electric needle acupuncture) for more than 6 mo were considered for the study. Exclusion criteria: Patients with a history of pruritus or dermatologic disease antedating renal failure, and those with skin disease other than the usual cutaneous findings of uremia such as xerosis or ecchymosis, and lesions due to scratching were excluded. Also, patients with systemic disease such as malignancy, cholestatic liver disease, or those under treatment with steroids or opiate analgesics were excluded.	(undergoing HD or PD treatment) and substantial pruritus	days washout between treatments	between treatments	Dropout of three more patients was caused by one case of lower limb amputation in a patient with diabetic gangrene that necessitated cessation of naltrexone therapy (during naltrexone period), one case of cerebral ischemia (during placebo period), and one case of renal transplantation	During the **naltrexone period, pruritus decreased by 29.2%** (95% CI, 18.7 to 39.6) on the VAS (after 4 weeks) During the **placebo period, pruritus decreased by 16.9%** (95% CI, 6.8 to 26.9) on the VAS (after 4 weeks → non-significant difference 2) Pruritus: Pruritus questionnaire (Severity, Distribution, Sleep disturbance) 3) Side effects Naltrexone: gastrointestinal upsets (nausea, loss of appetite): 9 patients (39.1%) Placebo: gastrointestinal upsets: 1 patient (4.3%) →Significant difference	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Legroux-Crespel (2004) **Uremic pruritus** **Naltrexone versus Loratadine**	Type of study: Multicenter randomized controlled trial Country: France Source of funding: No information provided. Inclusion criteria: Inclusion criteria were pruritus (from 1 month or more (the mean duration of pruritus was 40.05 months (from 1 to 300 months)) in patients with chronic renal failure, hemodialysis and age superior to 18 years. Exclusion criteria: Exclusion criteria were all other possible causes of pruritus, pregnancy, lactation, hypersensitivity to naltrexone or loratadine, dependency on opioids and severe liver insufficiency.	N total at baseline (n analysed): N= 52 patients. There was no significant difference between the two groups for sex, age, nephrological diagnosis, characteristics of dialysis, characteristics of pruritus (duration, intensity), other treatments or biological variables (especially urea, creatinine and phosphate). The mean score of pruritus on day 0 was 4.85.	Naltrexone (50 mg/day)	Loratadine (10 mg/day)	Length of follow up: 2 weeks Loss to follow up: Altogether 10 patients with naltrexone (4 for vertigo, 3 for nausea, 1 for malaise, 2 for cramps, 1 for sleeping disturbances and 1 for anorexia) and with loratadine (1 for vomiting, 1 for malaise, 1 without relation with loratadine) were withdrawn from the study	Evaluation of all studied criteria (pruritus, quality of sleep, adverse events, biological examinations) was made on days 0, 7 and 14. 1) Pruritus: The severity of pruritus and the sleep disturbance were measured by a visual analogue scale (VAS, 10 point scale) The mean score of pruritus on **day 0 was 4.85**. On day 7, the mean score of pruritus was **4.54 for patients with naltrexone** and **3.96 for patients with loratadine** But 7 patients had a dramatic regression of pruritus on day 7 and day 14 (>3 units: marked improvement) with naltrexone (4 on day 7 and 5 on day 14 because of 2 withdrawals 2) Side effects:	

						- Naltrexone induced 30 adverse events in 15 patients - Loratadine induced 3 adverse events in 2 patients	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Wolfhagen (1997) **Cholestatic pruritus** **Naltrexone versus placebo**	Type of study: Randomized double blind, Placebo-Controlled Study Country: The Netherlands Source of funding: No information provided. Inclusion criteria: All patients had persistent generalized pruritus without major fluctuations or symptom-free periods the preceding 3 months. Exclusion criteria: In all cases, the following conditions were excluded: use of opiates or deterioration of liver function test results during the last 3 months, renal failure (creatinine >150 mmol/L), changes in antipruritic medication (e.g., cholestyramine, rifampicin, antihistamines, ursodeoxycholic acid) within 1 month of entry, and pruritus primarily due to nonhepatological disorder	N total at baseline (n analysed): 16 patients were included in this study. Age: Naltrexone: range 37-72 years (mean: 58) Placebo: range 43-74 years (mean: 46) Sex (male/female): Naltrexone: 1/7 Placebo: 3/5 Underlying disease(s): Naltrexone: PBC (n = 8) Placebo: PBC (n = 5), PSC (n = 2), unclassified (n = 1)	Naltrexone (50 mg) 1x/day for 4 weeks (8 patients)	Placebo 1x/day for 4 weeks (8 patients)	Length of follow up: 4 week Loss to follow up: In the naltrexone group, the dose was decreased to 25 mg for 1 patient on the seventh day due to side effects and *1 patient withdrew after 2 weeks because itching increased*.	1) Pruritus: (VAS, 100 point scale) Throughout the study, patients scored the severity pruritus each day on visual analogue scales VAS entry Naltrexon group Daytime: 65 (52-93) Nighttime: 59 (8-92) VAS entry Placebo group Daytime: 48 (18-80) Nighttime: 47 (7-80) Mean changes with respect to baseline were significantly different**, in favour of the naltrexone group, for daytime itching (-54% SEM 10 vs. 8% SEM 10; P < 0.001)** and **nighttime itching (-44% SEM 11 vs. 7% SEM 9, P = 0.003).** 2) Side effects **Four patients in the treatment group** experienced an initial period of general malaise, **associated with nausea (4 patients), dizziness (3),**	

						flushing (2), drowsiness (2), headache (1), nightmares (1), and tremor (1). These symptoms developed within the first 2 days and subsided or greatly improved after about 3 days, without additional treatment or withdrawal of medication. In 1 patient, the symptoms persisted and reduction of the dose to 25 mg/day after 1 week provided some relief, but the symptoms did not disappear. **Six patients (5 naltrexone, 1 placebo) reported mild abdominal cramps**, which in general were present during the whole treatment period. Other symptoms noted were dry mouth (naltrexone, 2; placebo, 1), increased peripheral edema (naltrexone, 1), night-sweating (naltrexone, 1), irritability (placebo, 1 epistaxis (placebo, 1), and swelling of the hands (1). 3) Quality of sleep and fatigue (both on VAS, 100 point scale) The naltrexone group, improvements in nighttime itching correlated well with the decrease in sleep (Rs =0.93; P<0.0001) and showed a trend with reduced fatigue (Rs = 0.71; P < 0.2)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Terg (2002) **Cholestatic pruritus** **Naltrexone versus placebo**	Type of study: Randomized, double blind, placebo-controlled crossover study Country: Argentina Source of funding: No information provided Inclusion criteria: The duration of pruritus ranged from 6 to 11 months. Eleven patients received ursodeoxycholic acid, three of them a combination of ursodeoxycholic acid and cholestyramine, one a combination of ursodeoxycholic and corticosteroids; one patient received ursodeoxycholic acid, cholestyramine, phenobarbital, ondansentron and rifampicin. All of them had taken their medicine for longer than 3 months without significant response to treatment. Four patients did not receive any specific antipruritic treatment at all. Exclusion criteria: Exclusion criteria encompassed the following: (1) use of opiates within the last 10 days; (2) changes in antipruritic medication within 1 month of entry; (3) serum	N total at baseline (n analysed): Twenty patients (36–70 years old) with pruritus associated with chronic intrahepatic cholestasis were included in this study Group A (naltrexone-placebo): 11 Group B (placebo-naltrexone): 9 Age: (mean ± SD) Group A: 55 ± 10, range 36-70 years Group B: 55 ± 9, range 42-69 years Sex (male/female): Group A:3/8 Group B: 0/9 Underlying disease(s): PBC (n = 15), chronic hepatitis C (n = 2), PSC (n = 1), overlap syndrome	Naltrexone (25 mg/d) 2x (9:00 h and 14:00 h)	Placebo (25 mg/d) 2x (9:00 h and 14:00 h)	Length of follow up: 6 weeks After a 1-week period in which baseline pruritus score was obtained, patients were randomized to receive pills containing 50 mg naltrexone (Group A) or identical pills containing placebo (Group B) during 2 weeks. After this time the treatment was stopped. A 1-week washout period ensued, and the subjects were crossed over to the other therapy for 2 additional weeks Patients with partial or complete response were included in an open study to receive naltrexone 50 mg/day for 2 additional months and were followed as outpatients every 2 weeks. Severity of pruritus was evaluated using the same scoring system as the short-term treatment. Loss to follow up: **Two patients abandoned the study on the third day during naltrexone treatment** period due to the persistence of side effects. Patient no. 17 started with asthenia, dizziness, nausea	1) Pruritus: (VAS, 10 point scale) The severity of pruritus was assessed daily for daytime and night-time complaints using a visual analogue scale for 1 week before starting treatment and during the 5 weeks of the study. Complete response was defined as disappearance of pruritus and partial response as >50% reduction in the pruritus score. Baseline pruritus score (VAS 10 cm): (mean ± SD) Group A: 6.27 ± 1.61 (daytime), 6.52 ± 2.42 (night-time) Group B: 6.32 ± 3.12 (daytime), 5.03 ± 2.48 (night-time) Results: **Mean daytime pruritus VAS** decreased from 6.29 **SE 2.28 to 3.55 SE 2.39**, P = 0:0003; and **night-time itchin**g improved **from 5.89**	

	creatinine . 1:5 mg/dl; (4) age , 18 years or pregnancy; (5) drug-induced cholestasis; (6) extrahepatic cholestasis.	(n = 1), cryptogenic cirrhosis (n = 1)			and vomiting during naltrexone treatment and patient no. 19 began with mild epigastric pain and sporadic vomiting during the washout period, before naltrexone treatment, and continued this way during naltrexone treatment, stopping the treatment on the third day	**SE 2.49 to 3.55 SE 2.42**, P= 0:001. For Group A, diurnal VAS went from 6.27 SE 1.61 to 3.91 SE 2.39, P = 0:01 and night VAS was reduced from 6.52 SE 2.42 to 3.89 SE 2.17, P = 0:02 For Group B diurnal itching went from 6.32 SE 3.10 to 3.06 SE 2.47, P= 0:01 and night itching decreased from 5.03 SE 2.48 to 3.05 SE 2.77, P= 0:02 On the other hand, changes during placebo intake were not significant compared to baseline values (daytime VAS:6.12 SE 2.34 to 5.20 SE 2.43, P= 0:07/night VAS: 5.98 SE 2.46 to 5.25 SE 2.49, P = 0:06). These changes were independent of the sequence of treatment (placebo or naltrexone). 2) Side effects The most frequent side effects were dizziness (10 patients), nausea (eight patients), vomiting (six patients), headache and abdominal cramps (five patients). Most of them did not require additional medication and side effects improved or disappeared	

						48 h after starting treatment. (See table 3)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Jung (2009) **Burn pruritus** **Naltrexone (only)**	Type of study: Prospective study 1 group (naltrexone), unrandomized, unblind, uncontrolled Country: South-Korea Source of funding: Not reported Inclusion criteria: Patients admitted to Hangang Sacred Heart Hospital for rehabilitation after recovery from burn wounds Exclusion criteria: Patients treated with opioids, those with abnormal liver functions, and those withholding consent for study involvement were excluded	N total at baseline (n analysed): The sample consisted of 19 subjects; 17 subjects were already being treated for itching with antihistamines, 9 were receiving antihistamines and gabapentin, and 1 was taking only gabapentine.	Naltrexone 25 mg, in absence of side effects the dose was increased to 50 mg after one day	Uncontrolled	Length of follow up: 2 weeks Loss to follow up: None	1) Pruritus: (VAS, 10 point scale) After 2 weeks of receiving naltrexone, patients were asked to rate the severity of their itching on a Visual Analog Scale and to compare the current severity with their retrospective rating of the severity before the trial of naltrexon. Subjects reported a statistically significant decrease in the severity of itching after 2 weeks of treatment with naltrexone (P = .001) from 9.0 (SD 1.5) to 5.9 (SD 2.5). Fourteen subjects reported improvements in their experience of itching, and five reported no change in this regard 2) Side effects Seven patients reported side effects, such as headaches, nausea, vomiting, and abdominal cramps.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
La Salle (2008) **Burn pruritus** **Naltrexone (only)**	Type of study: Prospective study 1 group (naltrexone), unrandomized, unblind, uncontrolled Country: Canada Source of funding: Not reported Inclusion criteria: Burn patients with significant complaints of itch despite traditional therapy (H1/H2 receptor antagonist or hydrating lotion). Exclusion criteria: Patients not eligible for the trial included those who were taking opioids and any with abnormal liver function tests.	N total at baseline (n analysed): 13 burn subjects	Naltrexone 50 mg/day, 1 patient 100 mg/day	Uncontrolled	Length of follow up: 2 weeks Loss to follow up: Two discontinued naltrexone very soon after starting treatment, one because of an allergic reaction that was later shown, by sensitivity testing, to be due to the dye in the pills, and the other because of intolerable dizziness, therefore; they were excluded from the data analysis.	1) Pruritus: (VAS, 10 point scale) Among the patients (n = 8) who rated their itch before and 2 weeks after naltrexone administration, no statistically significant change was evident in their intensity ratings for "now" (1.9 ± 1.5 vs. 1.3 ± 1.0, p = 0.25) or "at its best" (0.5 ± 0.7 vs. 0.2 ± 0.2, p = 0.16), although itch reduction occurred in both categories. 2) Side effects One patient discontinued naltrexone because of intolerable dizziness However, 38% reported side-effects, including difficulty sleeping (23%), anxiety (8%), and hair loss (8%). 3) QoL Although, only 15% stated they were able to do more (cooking and sports), 62% disclosed that it improved their quality of life (31% were less stressed, 15% were able to sleep better, 8% were less irritable, and 8% announced improvement of their skin condition).	Five patients didn't score their VAS before naltrexone treatment

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Malekzad (2009) **Pruritus due to atopic eczema** **Naltrexone versus placebo**	Type of study: Randomized, double-blind, placebo-controlled study Country: Iran Source of funding: This study and the authors were not supported by any company with a vested interest in the product being studied and the project was funded by Skin Research Center Inclusion criteria: Inclusion criteria encompassed the following: (1) AE with pruritus; (2) no opiate dependency or use in pervious 2 weeks; (3) no evidence of any acute or chronic liver or renal disease Exclusion criteria: Patients who took opiates or any extra antipruritics including antihistamines, sedatives or systemic corticosteroids and those who did not wish to continue with the study were excluded from further analysis.	N total at baseline (n analysed): 38 patients with pruritic eczema Participants were between 24 and 85 years old. There were 10 male and 8 female in the naltrexone group and 11 male and 9 female in the placebo group. Mean age in the naltrexone group was 45.3 ± 12.9 years (mean rank = 19.2) and in the placebo group was 44.9 ± 13.9 years (mean rank = 19.8). Local corticosteroids were prescribed in four patients in the naltrexone group and six patients in the placebo group.	25 mg naltrexone twice daily (18 persons)	Identical capsules containing placebo twice daily (20 persons)	Length of follow up: 2 weeks Loss to follow up: One week after the beginning of the study, three patients in the naltrexone group and two patients in the placebo group discontinue their medications and the trial.	1) Pruritus (VAS 10 cm) The severity of pruritus was assessed daily complaints using a visual analogue scale (VAS) at the beginning of the study and in visits at the end of the 1st and 2nd week of the study. A scale of 0–10 was used and noted in an individual note. Mean VAS score at the beginning of the study in the naltrexone group was 8.11 ± 1.4 and in the placebo group was 7.8 ± 1.6. At the end of the first week, the mean VAS score was 3.3 ± 1.6 in the naltrexone group and was 5.6 ± 2.1 in the placebo group. There is a significant difference between two groups based on Mann–Whitney U-test (P < 0.005). Mean VAS score 2 weeks after intervention in the naltrexone group was 1.3 ± 1.4 and in the placebo group was 4.5 ± 2.8; hence, there is a significant difference between the two groups (p<0.001)	

						2) Side effects Two patients in the naltrexone group reported drug side-effects including sedation and nausea, while one patient in the placebo group complained from nausea. There was not a significant difference between two groups in this matter.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Metze (1999) **Pruritus due various causes** **Naltrexone (only)**	Type of study: Prospective study 1 group (naltrexone), unrandomized, unblind, uncontrolled Country: Germany Source of funding: Not reported Inclusion criteria: Patients with severe pruritus Exclusion criteria: Not reported	N total at baseline (n analysed): A total of 50 patients with severe pruritus (18 men, 32 women; age, 25 to 93 years; median, 63.4 years) Some of the patients had persistent pruritus, either localized or generalized, caused by liver cirrhosis (n = 1), chronic renal failure (n = 2), diabetes mellitus (n = 2), hydroxyethyl starch (HES) (n = 4), and contact with water (n = 1). Five patients complained of a generalized pruritus on noninflamed skin where the origin could not be determined. Other patients were treated for pruritic symptoms caused by skin disorders such as primary cutaneous lymphoma (4 cases of mycosis	A single daily oral dose of 50 mg naltrexone	Uncontrolled	Length of follow up: Thirty-seven patients received naltrexone for more than 4 weeks, that is, 5 weeks to 2 months (n = 12), 3 to 6 months (n = 17), 7 to 12 months (n = 5), 13 to 20 months (n = 3). Loss to follow up: Consequently, 3 patients were withdrawn from the study because of total failure of naltrexone	1) Pruritus (VAS 10 cm) The patients were asked to daily record the estimated average intensity of the pruritus on a visual analogue scale before and during therapy. A significant therapeutic response was achieved in 35 of the 50 patients within 1 week (confidence limits of 0.55 and 0.82 at a confidence level of 0.95). Naltrexone was of high antipruritic effect in 9 of 17 cases of prurigo nodularis and contributed to healing of the skin lesions. 13 of the 50 patients who received naltrexone experienced a complete	

		fungoides, 1 case of follicular B-cell lymphoma), atopic dermatitis (n = 4), xerosis cutis (n = 2), bullous pemphigoid (n -- 1), psoriasis (n = 1), lichen sclerosus et atrophicus (n = 1), scabies (n = 1), arthropod reaction (n = 1), macular amyloidosis (n = 1), lichen sim- plex chronicus (n = 1), and prurigo nodularis (n = 17). With regard to the cause of prurigo nodularis, diabetes mel- litus could be diagnosed in 3 patients, chronic lymphatic leukemia in 1 patient, and psychologic disorders in another 7 patients. In 39 of 50 cases pruritus was refractory to therapeutic attempts using sedatives, antihistamines, antipruritic lotions containing polidocanol or menthol, and UVA/UVB irradiation				elimination of pruritus (antipruritic effect of 100%), 13 experienced a reduction of the pruritus intensity of 50% and more, and 9 had a reduction of less than 50%. In 15 of 50 patients, no improvement of the pruritic symptoms could be achieved. Upon statistical evaluation of visual analogue scores 2) Side effects Eleven patients complained of mild to severe nausea that could be easily managed by oral administration of metoclopramide. Three patients reported fatigue, 1 patient each suffered from dizziness, heartburn, and diarrhea	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Lee (2016) **Pruritus in older patients due to various causes** **Naltrexone (only)**	Type of study: Prospective study 1 group (naltrexone), unrandomized, unblind, uncontrolled Country: South Korea Source of funding: Not reported	N total at baseline (n analysed): Sixteen patients with antihistamine-resistant severe pruritus were enrolled. The mean age of the patients was 73 years (range, 65 to 83 years), and the men-to-women ratio was 6:4..	Patients received 50 mg of naltrexone per day. * Patients were instructed to continue their previous therapies including systemic corticosteroids, phototherapies, extra antipruritics, topical corticosteroids, and emollients.	Uncontrolled	Length of follow up: approximately 2 months (average, 66.5 days) Loss to follow up: No dropouts	1) Pruritus (VAS 10 cm) Efficacy was assessed with a VAS ranging from 0 (no pruritus) to 10 (the most intensive pruritus they can imagine)2 and scored at the beginning, after 2 weeks, and at the end of the 2-month naltrexone treatment According to the VAS scores, 13 (72.2%) of 18 patients reported a	

	Inclusion criteria: Patients 65 years and older with severe pruritus (a visual analogue scale [VAS] score 7 or higher). Exclusion criteria: No exclusion criteria reported	All the patients had persistent itching sensation, either generalized or localized, caused by prurigo nodularis, cholestatic pruritus due to cholestatic liver disease, uremic pruritus, eczema senilis, and cutaneous lymphoma. Some of the patients had pruritus of unknown origin.				"much improved" condition, experiencing more than 50% reduction in pruritus intensity (Table 1, Fig. 1). Among them, 6 (33.3%) reported an almost complete elimination of pruritus, with a VAS score of 0 or 1. Sixteen (88.9%) of 18 patients showed symptomatic improvement, and only 2 (11.1%) had persistent pruritus. The initial mean VAS score was 8.28±0.89, and at the end of the second week, the mean VAS score significantly decreased to 3.72±1.49 ($p < 0.05$). Finally, at the end of 2 months, the mean VAS score was again significantly lower (2.83±1.98), compared with both the initial VAS score and the VAS score at the end of the second week ($p < 0.05$). There was no statistically significant difference in drug efficacy related to the cause of pruritus (p =0.507 2) Side effects Five patients had side effects including insomnia (two patients), fatigue, constipation, and anorexia.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments

Kronsten (2013) **Cholestatic pruritus in pediatric patients with Alagille syndrome (AGS)** **Multiple treatment modalities (Naltrexone, n =14)**	Type of study: Retrospective review Country: United Kingdom Source of funding: Not reported Inclusion criteria: Patients with AGS Exclusion criteria: Not reported	N total at baseline (n analysed): A total of 62 patients (34 boys, 28 girls) with AGS were included. The median age of patients at the time of the study was 7 years 8.5 months (range 5 months-18 years 10 months).	Naltrexone was prescribed at a dose of 0.25-0.5 mg/kg once daily. The median dose was 3 mg/day (range 2.5-12.5 mg/day). 14/62 patients were treated with Naltrexone	Uncontrolled.	Length of follow up: Unclear Loss to follow up: Retrospective cohort	1) Pruritus Pruritus was graded on a 4-point scale: none, mild, moderate or severe. The antipruritic drug efficacy was graded on a 5-point scale based on physician's, family's, and patient's documented opinion. A drug was classed as having "no effect" if no change in pruritus was reported; a "minimal effect" if there was some reported improvement, but a new drug was commenced immediately; "some effect" if there was a significant improvement in pruritus, but combination therapy was still necessary; a "good effect" if there was a definite improvement in pruritus without add-on therapy; and a "very good" effect if the drug controlled pruritus as a monotherapy. Effect naltrexone in 14 patients: No effect – 2 patients Minimal effect - 1 patient Some effect – 5 patients Good effect – 6 patients 2) Side effects Four (28.6%) complained of adverse effects: 2 experienced nausea and irritability, 1 had diarrhoea, and 1 experienced severe abdominal pain.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Van Os-Medendorp 2007 **Chronic pruritus** **Nursing programme 'Coping with itch' vs standard medical care (SMC)**	Type of study: Randomised, controlled trial Country Netherlands Source of funding: None Inclusion criteria: patients with chronic pruritic skin diseases, regardless of the specific diagnosis, who were age 18 years or older, and who visited the dermatology outpatient department Exclusion criteria: Unmentioned	N total at baseline (n analysed): 120 Baseline characteristics: No significant differences were found between the characteristics of the intervention group and the control group or in the baseline measures. The mean age of the patients was about 56 years and most patients were female. The educational level was mostly low or medium. The most frequently reported diagnoses were eczema, atopic dermatitis and pruritus. The mean duration of the skin disease was about 16 years, the mean duration of itch was 12 years. Most patients had a high frequency and intensity of itching and scratching at baseline.	N = 63 Usual medical care from a dermatologist as well as nursing care according to the programme 'Coping with Itch* **: Educational and cognitive behavioural interventions, such as individual patient education, awareness training and habit reversal, relaxation exercises and psychosocial support.*	N = 57 Usual medical care from a dermatologist; diagnosis, therapeutic interventions such as emollients and topical steroids.	Length of follow-up: 9 months; data collection at baseline (t0), 3 months (t1) and 9 months (t2) Loss-to-follow-up: In summary: at t1 data of 29/63 patients in the intervention group and 36/57 patients in the control group was used. At t2, usable data for 23/63 intervention group patients and 28/57 control group patients was present.	**1) Pruritus:** (see Comments →) t0: high intensity of itching/scratching group A: 20/25 (80%) group B: 25/32(78%) t1: high intensity of itching/scratching group A: 14/25 (56%) group B 19/32 (59%) t2: high intensity of itching/scratching group A: 12/24 (50%) group B: 16/29 (55%) No significant differences were found between the groups **2) Quality of life:**	Primary outcome was measured as frequency and intensity of itching and of scratching. The 4 factors were reduced tot 2; frequency of itching/scratching and intensity of itching/scratching. Afterwards these were converted to a dichotomous measure; high (>4) and low (<4) frequency of itching/scratching and high (>3) intensity and low (<3) intensity of itching/scratching.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Pour-Reza-Gholi (2007) **Uremic pruritus** **Doxepin 10mg 2dd1 versus placebo**	Type of study: Randomized placebo-controlled, double-blinded, crossover study. Country: Iran Source of funding: Supported by Pakhshe Razi (Tehran, Iran) as supplier of Doxepin capsules visually identical to placebo medication Inclusion criteria: Patients with severe generalised pruritus on hemodialysis; 3 times a week with a Kt/V > 1.2, serum calcium levels less than 11.5 mg/dL, serum phosphate levels less than 6.5 mg/dL, serum intact parathyroid hormone between 13.0 pg/mL and 66.0 pg/mL, serum aluminum between 0 and 6 ng/mL, serum magnesium less than 2.6 mg/dL, and blood hemoglobin level greater than 10 mg/dL Exclusion criteria: Administration of anti-pruritic drugs a week prior to the study and hemodialysis due to acute renal failure	N total at baseline (n analysed): 24(23) patients on hemodialysis with severe generalized pruritus	Doxepin 10mg 2x/d for 1wk After 1 week crossover to placebo 1x/d with 7 days washout between treatments	Placebo 1x/d for 1wk After 1 week crossover to Doxepin 10mg 2x/d with 7 days washout between treatments	Length of follow up: Unclear Loss to follow up: 1 due to adverse event	Pruritus: subjective assessment by asking participants to score their pruritus as completely improved, relatively improved or unchanged/worsened. Complete improvement in 14 (P < .001) for the intervention group, 1 in the control group Drowsiness was the main complaint reported by 12/24 patients (50.0%), leading to 1 patient refusing to continue drug administration.	Scarce information on analysis of results, no analysis on adverse events. 1 loss of follow up due to adverse event; analyzed as complete improvement in placebo group and no effect of doxepin

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Shohrati (2007) **Pruritus due to sulfur mustard** **Doxepin vs Cetirizine vs Hydroxyzine**	Type of study: A randomized , double-blind clinical trial Country: Iran Source of funding: No mention of funding in this study Inclusion criteria: Male gender, being a chemical-exposed veteran, having established SM-resulted pruritus for longer than 6 months and being available for further evaluation Exclusion criteria: Itching resulted from systemic or non-chemical induced skin diseases and history of any anti-pruritic treatment 3 months prior to the onset of the study. Patients who developed drug complication and/or hypersensitivity reactions during the study were also immediately excluded.	N total at baseline (n analysed): 68-70 sulfur-mustard veterans(male) with pruritus (after documented skin exposure to SM) The average of patients was 44.3+-6.3 years old in the Cetirizine group, 42.3+-5.4 in the Doxepine group, and 41.1+-6.2 in the Hydroxyzine group (P = 0.756). The mean initial pruritic scores in Cetirizine, Doxepine, and Hydroxyzine group were 38.2+-4.8, 37.2+-4.9, and 37.3+-5.1, respectively (P = 0.854). The age and severity of pruritus were not different among groups at the beginning of the study.	Hydroxyzine 25mg 1x/d for 4wk Cetirizine 10mg 1x/d for 4 wk Doxepin 10mg 1x/d for 4 wk	Not applicable	Length of follow up: 8 weeks Loss to follow up: Unmentioned in study, the results however show a high probability	1. Pruritus: Scored by calculating a Pruritic score (maximum of 48 points) and then categorized patients into 3 groups based on itching severity. Mild (1-16 points), Moderate (17-32 points), Severe (33-48 points) Successful treatment defined as a decrease rate of more than 5 scores in the Pruritic score. No statistical significance was found after comparison of Cetirizine, Doxepine and Hydroxyzine final pruritic scores. 2. Complications (=Adverse effects); 14 patients complained of sedation in the Doxepin group, 6 in the Cetirizine group, 18 in the Hydroxyzine group (P=0.238). 2 patients in each of the groups showed dizziness (P= 0.974) A statistically significant association between drug-	

						induced sedation and therapeutic efficacy of the drugs was found (P= 0.035). No further breakdown was given.	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Foroutan (2017) **Uremic pruritus** **Doxepin vs Pregabaline**	Type of study: Multicenter single blind randomized trial Country: Iran Source of funding: The study was supported by Kerman University of Medical Sciences Inclusion criteria: Patients on hemodialysis aged 16–80 years who were suffering from pruritus Exclusion criteria: Patients with hepatic failure, hyperthyroidism, narrow angle glaucoma, heart block, decompensated heart failure, hypotension (defined as systolic blood pressure less than 90 mmHg), history of allergy to pregabalin or doxepin, uncontrolled psychiatric diseases, myocardial infarction in the past three months, epilepsy, or even one episode of seizure and pregnant patients were excluded from the study. Moreover, patients with psoriasis, atopic dermatitis or any other	N total at baseline (n analysed): N= 90(72) patients. There were no significant differences between the baseline characteristics of the patients in the two groups.	Doxepin (10 mg/day)	Pregabaline (50 mg/day)	Length of follow up: 4 weeks Loss to follow up: Doxepin group: 9/44 (20,5%) 1 due to intolerable adverse effects 3 due to poor collaboration with the research team 1 due to heart surgery 1 due to heart attack Pregabalin group: 9 /46 (19,5%) 3 due to intolerable adverse effects	The severity of the pruritus and its impact on the quality of life were assessed at baseline and after 1 week, 2 weeks, and 4 weeks of the intervention using the VAS, 5-D itch scale and Dermatology Life Quality Index (DLQI), respectively. 1) Pruritus: As a scale for the assessment of itch severity, the VAS was used. Baseline VAS: pregabalin 7,5 +/- 1,4 and doxepin 7,1 +/- 1,3 (P = 0,296) Week 4 VAS: pregabalin 2,1 +/- 2,6 and doxepin 4,4 +/- 2,4 (P = 0,001) 2) DLQI: The DLQI is a questionnaire commonly used to assess the impact of various dermatologic diseases and conditions such	

	condition that can justify the pruritus were not included in the study.				3 due to poor collaboration with the research team 2 due to kidney transplantation 1 due to death	as pruritus on the quality of life. Baseline DLQI: pregabalin 3,8 +/- 1,8 and doxepin 3,6 +/- 1,4 (P = 0,551) Week 4 DLQI: pregabalin 1,2 +/- 1,5 and doxepin 2,2 +/- 1,4 (P = 0,007) 3) Adverse effects: Somnolence was the most reported adverse effect in both groups with 6 patients in the pregabalin group (16,2%) and 5 patients in the doxepin group (14,2%) Other adverse effects: Doxepin: nervousness (1) Pregabaline: edema (3), drowsiness (3), imbalance during walking (1), numbness (1)	

Tabellen karakteristieken geselecteerde studies UVB (2020)

Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**		**Outcome measures and effect size**	**Comments**
Ko 2011 **Uremic pruritus**	Type of study: Single-blind, randomised, controlled trial	N total at baseline (n analysed): 	N = 11 (10 analysis) NB-UVB for the whole body surface, 3x / week	N = 10 (8 analysis) Time-matched exposures to long-wave UVA. The	Length of follow-up: 12 weeks; 6 weeks of		**1) Pruritus:** VAS score (0-10), assessed at baseline, then	

Narrowband UVB vs (time-matched) UVA radiation	Country Taiwan Source of funding: financially supported by a research grant from the National Taiwan University Hospital, Yun-Lin Branch Inclusion criteria: Aged > 18 years, with CKD stage III-V. Patients with a VAS score > 5 and itching duration of longer than 2 months were enrolled. Exclusion criteria: Pregnancy or breastfeeding, history of photosensitivity.	21 Baseline characteristics: 11 men, 10 women. 14 on maintenance hemodialysis, 3 on maintenance peritoneal dialysis, 4 free from dialysis throughout the study period. All participants were unresponsive to oral antihistamines and topical emollients for their pruritus.	(for 6 weeks). Start: 210 mJ cm-2, increased by 10% each time	doses of UVA were approximately 1-6 J cm-2.	treatment. Week 7-12 follow-up Loss-to-follow-up: 1 in I-group discontinued. 2 in C-group discontinued.		weekly until week 12. Reported as decrease in VAS. Pruritus characteristics were assessed by the McGill Pain Questionnaire; At baseline and at week 6 VAS scores at week 6 decreased by **3.53** units [95% CI 6.02–1.03] and **3.38** units (95% CI 5.54–1.21) in the NB-UVB and control groups, respectively. However **no statistical significance** between the two groups. **2) Side effects** none reported.	
Wang 2013 **Uremic pruritus** **Narrowband UVB vs "prior pruritus treatment"**	Type of study: Controlled trial, quasi-experimental design. Country Taiwan Source of funding:	N total at baseline (n analysed): 43 (42) Baseline characteristics: 22 women, 20 men. Mean age of participants 62.9 years	N = 21 NB-UVB for the whole body surface, 3x / week (for 2 weeks). Start: 100 mJ cm-2, increased by 20 mJ/cm^2 each time (up to 220 mJ/cm^2) Participants in both	N = 21 "Participants in both groups were maintained on their prior pruritus regimens, including topical corticosteroids and antihistamines."	Length of follow-up: 2 weeks Loss-to-follow-up: 1 drop-out in intervention group (G.I. bleeding requiring hospitalisation,		**1) Pruritus:** VAS score (0-10), assessed at 7 times, (unclear at what interval, likely after each intervention.) Baseline intervention group: 6.62 (1.43 SD)	

	None <u>Inclusion criteria</u>: Aged 18 or older. Diagnosed with end-stage renal disease. Underwent maintenance haemodialysis > 3months. Pruritus appeared after the ESRD diagnosis and had moderate/high pruritus even after receiving topical emollients, corticosteroids and oral antihistamines (VAS 4 or more) <u>Exclusion criteria</u>: Pruritus that could be explained by other systemic, dermatological or psychological causes. Changes in consciousness.	All participants were unresponsive to oral antihistamines and topical emollients for their pruritus.	groups were maintained on their prior pruritus regimens, including topical corticosteroids and antihistamines. 20/21 used oral antihistamines. 18/21 used emollients. 3/21 used steroids. 3/21 used menthol.	19/21 used oral antihistamines. 17/21 used emollients. 3/21 used steroids. 1/21 used menthol.	unrelated to intervention)		Baseline control group: 6.14 (1.23 SD) (p = 0.26) VAS at measure moment seven for intervention group: 2.09 (1.84 SD) control group: 5.57 (1.86 SD) (P<0.001) **2) Side effects:** None reported	

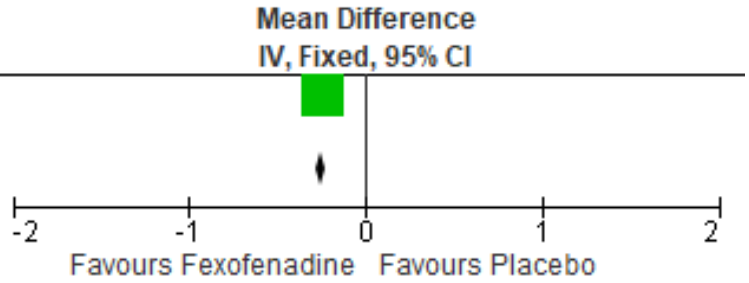
Sherjeena 2017 **Uremic pruritus** **Narrowband UVB vs oral cetirizine**	Type of study: Controlled trial Country India Source of funding: none Inclusion criteria: Aged > 18 years, with CKD stage IV-V. Patients with a VAS score > 5 were enrolled. Itch appeared in a regular pattern during preceding six months. Exclusion criteria: History of photosensitivity, early renal disease (stage I-III), pregnancy and lactation. Pruritus secondary to other skin or systemic diseases.	N total at baseline (n analysed): 30 (30) Baseline characteristics: 22 women, 20 men. Mean age of participants 62.9 years All participants were unresponsive to oral antihistamines and topical emollients for their pruritus.	N = 15 Narrowband UVB every third day for 15 sessions.(6 weeks) No topical emollients or oral antihistamines were used. Starting dose 200 mJ/cm^2, increased by 10% every session to a maximum of 1038 mJ at the end of 15 sessions.	N = 15 Topical liquid paraffin and oral cetirizine 10mg once a day	Length of follow-up: 6 months, intervention applied for 6 weeks Loss-to-follow-up: None		**1) Pruritus:** VAS score (0-10), assessed at baseline, 4 weeks, 3 months and 6 months. Baseline group A: 9.13 (0.4 SD) and group B: 9.1 (0.6 SD) 4 weeks group A: 1.9 (0.4 SD) and group B: 8.8 (0.7 SD) (p = 0.025) 3 months group A: 1.9 (0.4 SD) and group B: 8.8 (0.7 SD) (p = 0.025) 6 months group A: 2.4 (0.8 SD) and group B: 8.8 (0.7 SD) (p = 0.025) **2) Side effects:** None reported	

Bijlage 7: Literatuuranalyse

Antihistaminica (2020): Meta-analyse

Study or Subgroup	Fexofenadine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kawashima 2003	-0.75	0.13	201	-0.5	0.12	199	100.0%	-0.25 [-0.27, -0.23]
Total (95% CI)			**201**			**199**	**100.0%**	**-0.25 [-0.27, -0.23]**

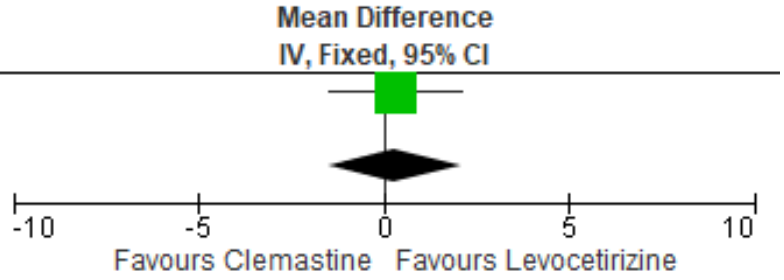
Heterogeneity: Not applicable
Test for overall effect: Z = 19.99 (P < 0.00001)



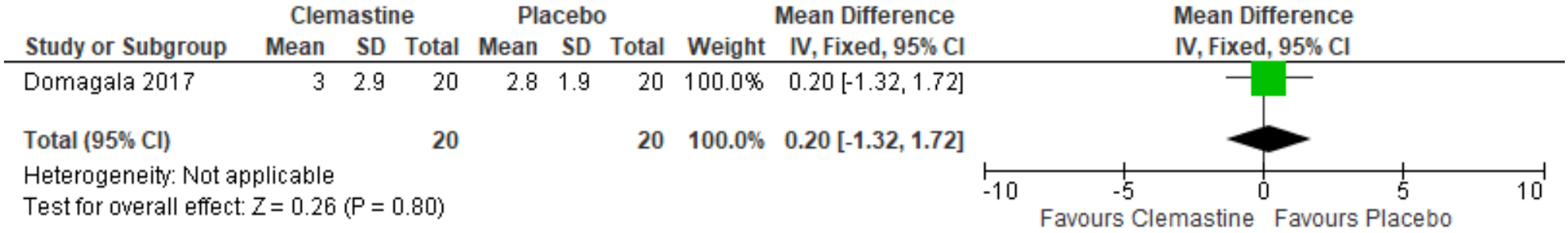
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Pruritus in AD (fexofenadine vs placebo) - VAS 4 weeks.

Study or Subgroup	Clemastine Mean	SD	Total	Levocetirizine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Domagala 2017	3	2.9	20	2.7	3	21	100.0%	0.30 [-1.51, 2.11]
Total (95% CI)			**20**			**21**	**100.0%**	**0.30 [-1.51, 2.11]**

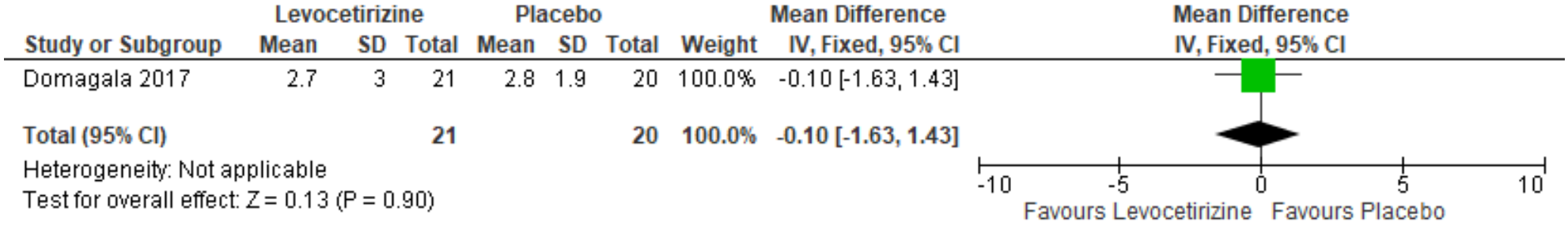
Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)



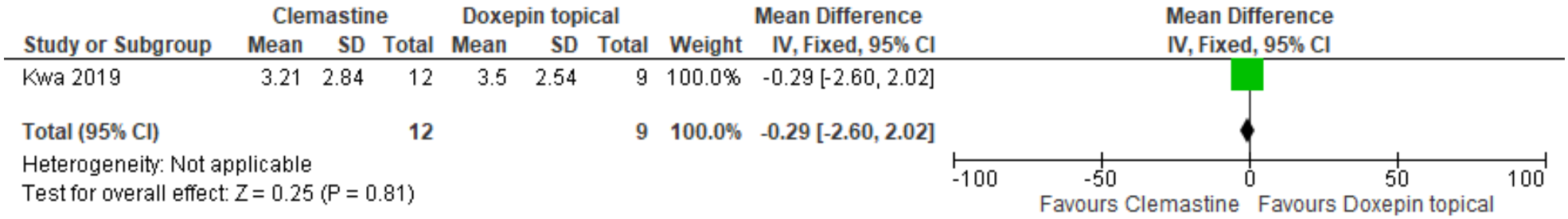
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Pruritus in Psoriasis (clemastine vs levocetirizine) - VAS 7 days.



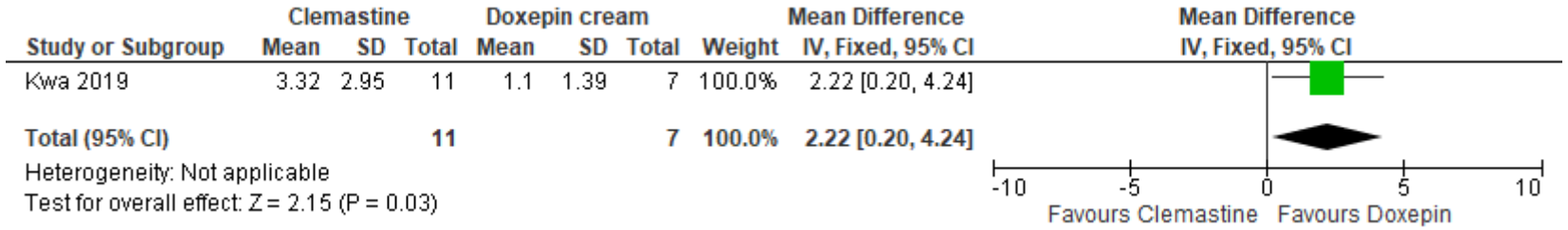
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Pruritus in Psoriasis (clemastine vs placebo) - VAS 7 days.



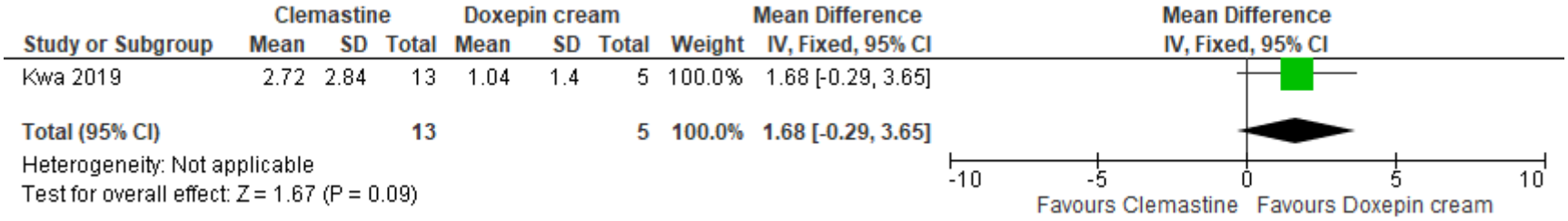
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Pruritus in Psoriasis (lev vs plac) - VAS 7 days.



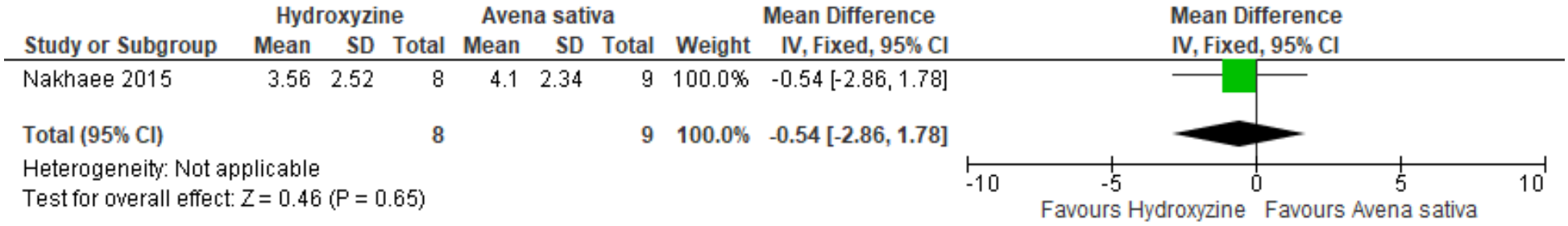
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Post-burn pruritus (clem vs dox cream) - VAS 2 weeks



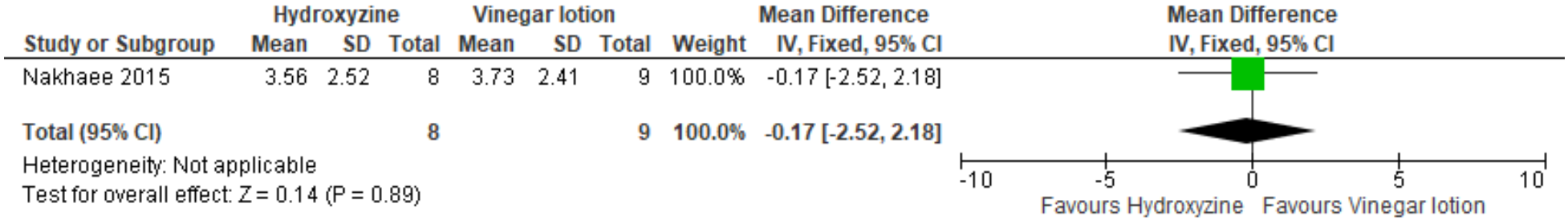
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Post-burn pruritus (clem vs dox cream) - VAS 6 weeks



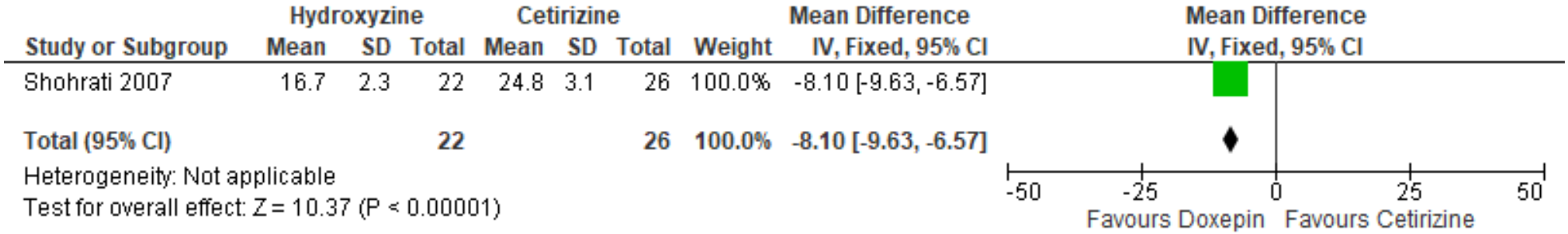
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Post-burn pruritus (clem vs dox cream) - VAS 12 weeks



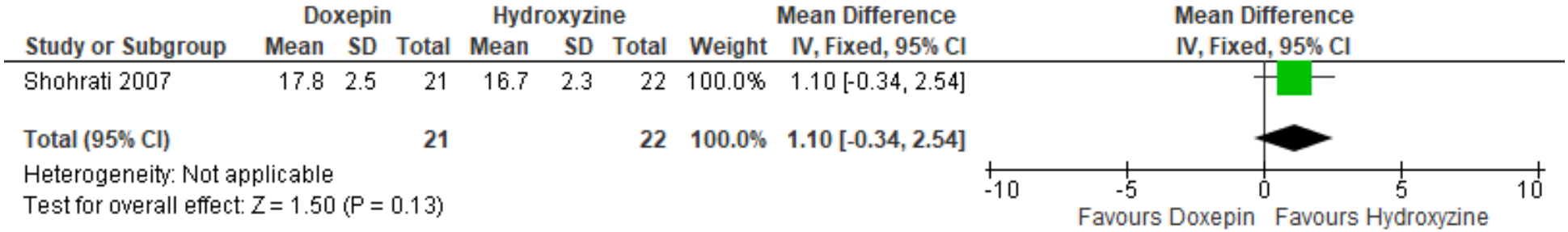
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Uremic pruritus (hydr vs avena) - VAS 7 weeks.



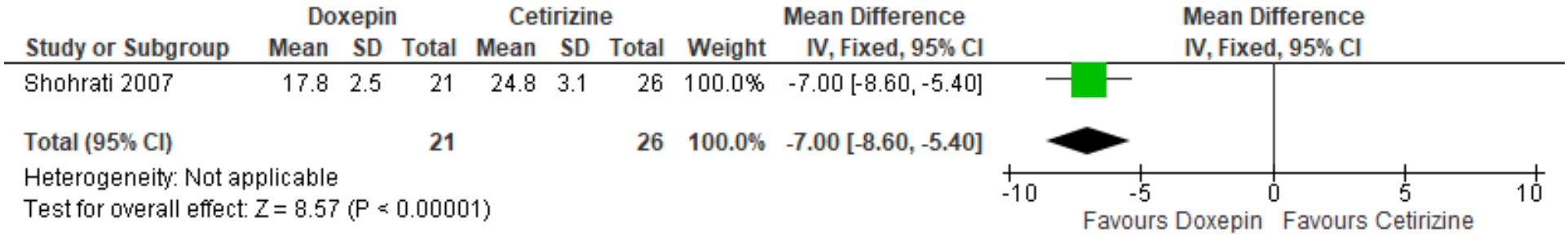
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Uremic pruritus (hydr vs vineg) - VAS 7 weeks.



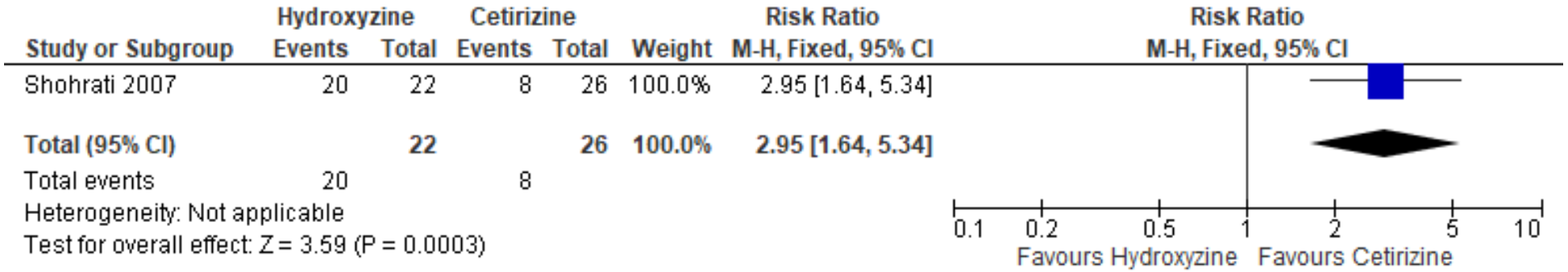
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Pruritus from SM (hydroxyzine vs cetirizine) - Pruritus score 8 weeks



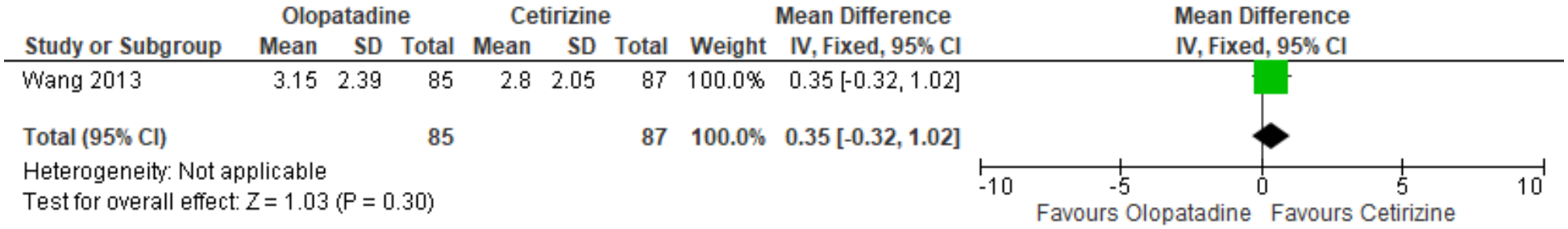
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Pruritus from SM (doxepin vs hydroxyzine) - Pruritus score 8 weeks



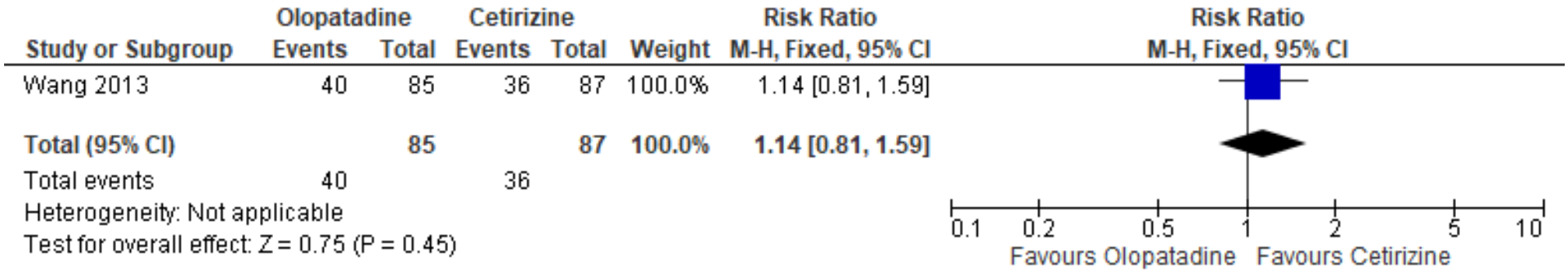
Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Pruritus from SM (doxepin vs cetirizine) - Pruritus score 8 weeks



Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Pruritus from SM (hydroxyzine vs cetirizine) - 1 or more adverse events 8 weeks.



Forest plot of comparison: Pruritus in AD, outcome: Cutaneous Pruritus (olop vs cet) - VAS 2 weeks. No significant differences between the groups



Forest plot of comparison: Antihistaminics for Chronic pruritus, outcome: Cutaneous Pruritus (olopatadine vs cetirizine) - 1 or more adverse events 2 weeks.

GRADE Summary of Findings (SoF) tabellen Antihistaminica

Auteur(s): Kawashima et al 2003
Vraagstelling: Fexofenadine versus placebo voor Pruritus in AD

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Fexofenadine	placebo	Relatief (95% CI)	Absoluut (95% CI)		
Pruritus in AD (fexofenadine vs placebo) - VAS 4 weeks (Scale from: 0 tot 10)												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Fexofenadine	placebo	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	ernstig [a]	niet ernstig [b]	niet ernstig	niet ernstig	niet gevonden	201	199	-	MD **0.25 lager** (0.27 lager tot 0.23 lager)	⊕⊕⊕◯ REDELIJK	BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Downgraded by 1 ; No explanation about any measurements taken to prevent varying types of bias.
b. Single study, impossible to grade inconsistency

Auteur(s): Domagala et al 2017
Vraagstelling: Clemastine versus Placebo / Clemastine versus Levocetirizine / Levocetirizine versus Placebo voor Pruritus in Psoriasis

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Clemastine	Placebo	Relatief (95% CI)	Absoluut (95% CI)		
Pruritus in Psoriasis - Clemastine versus placebo - VAS 7 days (Scale from: 0 tot 10)												
1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	niet ernstig	zeer ernstig [b]	niet gevonden	20	20	-	MD **0.2 hoger** (1.32 lager tot 1.72 hoger)	⊕⊕◯◯ LAAG	BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Single study; impossible to grade for inconsistency
b. Optimal information size not reached, CI crosses clinical decision threshold between recommending and not recommending intervention

Pruritus in Psoriasis - Clemastine vs Levocetirizine - VAS 7 days (Scale from: 0 tot 10)

1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	niet ernstig	zeer ernstig [b]	niet gevonden	20	21	-	MD **0.3 hoger** (1.51 lager tot 2.11 hoger)	⨁⨁◯◯ LAAG	BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Single study; impossible to grade for inconsistency
b. Optimal information size not reached, CI crosses clinical decision threshold between recommending and not recommending intervention

Pruritus in Psoriasis - Levocetirizine vs Placebo - VAS 7 days (Scale from: 0 tot 10)

1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	niet ernstig	zeer ernstig [b]	niet gevonden	21	20	-	MD **0.1 lager** (1.63 lager tot 1.43 hoger)	⨁⨁◯◯ LAAG	

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Single study; impossible to grade for inconsistency
b. Optimal information size not reached, CI crosses clinical decision threshold between recommending and not recommending intervention

Auteur(s): Kwa et al 2019
Vraagstelling: Clemastine versus Doxepin (topical) voor Post-burn pruritus

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Clemastine	Doxepin (topical)	Relatief (95% CI)	Absoluut (95% CI)		

Post-burn pruritus - Clemastine vs Doxepin (topical) - VAS 2 weeks (Scale from: 0 tot 10)

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Clemastine	Doxepin (topical)	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	ernstig [b]	zeer ernstig [c]	niet gevonden	12	9	-	MD **0.29 lager** (2.6 lager tot 2.02 hoger)	⊕◯◯◯ ZEER LAAG	NIET BELANGRIJK

Post-burn pruritus - Clemastine vs Doxepin (topical) - VAS 6 weeks (follow up: 6 weken; Scale from: 0 tot 10)

1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	ernstig [b]	zeer ernstig [c]	niet gevonden	11	7	-	MD **2.22 hoger** (0.2 hoger tot 4.24 hoger)	⊕◯◯◯ ZEER LAAG	NIET BELANGRIJK

Post-burn pruritus - Clemastine vs Doxepin (topical) - VAS 12 weeks (follow up: 12 weken; Scale from: 0 tot 10)

1	gerandomiseerde trials	niet ernstig	niet ernstig	ernstig [b]	zeer ernstig [c]	niet gevonden	13	5	-	MD **1.68 hoger** (0.29 lager tot 3.65 hoger)	⊕◯◯◯ ZEER LAAG	NIET BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Single study; impossible to grade for inconsistency
b. Comparison is a topical intervention
c. Optimal information size not reached, CI crosses clinical decision threshold between recommending and not recommending intervention

Auteur(s): Z. Çiftçi
Vraagstelling: Clemastine versus Doxepin (topical) voor Post-burn pruritus
Setting:
Literatuur:

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Clemastine	Doxepin (topical)	Relatief (95% CI)	Absoluut (95% CI)		
Post-burn pruritus - Clemastine vs Doxepin (topical) - VAS 6 weeks (follow up: 6 weken; Scale from: 0 tot 10)												
1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	ernstig [b]	zeer ernstig [c]	niet gevonden	11	7	-	MD **2.22 hoger** (0.2 hoger tot 4.24 hoger)	⨁◯◯◯ ZEER LAAG	NIET BELANGRIJK
Post-burn pruritus - Clemastine vs Doxepin (topical) - VAS 12 weeks (follow up: 12 weken; Scale from: 0 tot 10)												
1	gerandomiseerde trials	niet ernstig	niet ernstig	ernstig [b]	zeer ernstig [c]	niet gevonden	13	5	-	MD **1.68 hoger** (0.29 lager tot 3.65 hoger)	⨁◯◯◯ ZEER LAAG	NIET BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Single study; impossible to grade for inconsistency
b. Comparison is a topical intervention
c. Optimal information size not reached, CI crosses clinical decision threshold between recommending and not recommending intervention

Auteur(s): Nakhaee et al 2015
Vraagstelling: Hydroxyzine versus Avena sativa (Colloidal Oatmeal) / Hydroxyzine vs Vinegar lotion voor Uremic Pruritus

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Hydroxyzine	Avena sativa (Colloidal Oatmeal)	Relatief (95% CI)	Absoluut (95% CI)		
Uremic Pruritus - Hydroxyzine vs Avena Sativa (Colloidal Oatmeal) lotion - VAS 7 weeks (Scale from: 0 tot 10)												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Hydroxyzine	Avena sativa (Colloidal Oatmeal)	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	zeer ernstig [a]	niet ernstig [b]	ernstig	zeer ernstig [c]	niet gevonden	8	9	-	MD **0.54 lager** (2.86 lager tot 1.78 hoger)	⨁◯◯◯ ZEER LAAG	NIET BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Limitations in blinding of participants, personnel and outcome assessor; no double-blinding possible due to nature of interventions. The method of allocation concealment was not described.
b. Single study; impossible to grade for inconsistency
c. Optimal information size not reached, CI crosses clinical decision threshold between recommending and not recommending intervention

Uremic Pruritus - Hydroxyzine vs Vinegar lotion - VAS 7 weeks (Scale from: 0 tot 10)

1	gerandomiseerde trials	zeer ernstig [a]	niet ernstig [b]	ernstig	zeer ernstig [c]	niet gevonden	8	9	-	MD **0.17 lager** (2.52 lager tot 2.18 hoger)	⨁◯◯◯ ZEER LAAG	NIET BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Limitations in blinding of participants, personnel and outcome assessor; no double-blinding possible due to nature of interventions. The method of allocation concealment was not described.
b. Single study; impossible to grade for inconsistency
c. Optimal information size not reached, CI crosses clinical decision threshold between recommending and not recommending intervention

Auteur(s): Shohrati et al 2007
Vraagstelling: Hydroxyzine versus Cetirizine voor Pruritus from SM exposure

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Hydroxyzine	Cetirizine	Relatief (95% CI)	Absoluut (95% CI)		
Pruritus from SM exposure - Hydroxyzine vs Cetirizine - Pruritus score 8 weeks (Scale from: 0 tot 48)												
1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	zeer ernstig [b]	ernstig [c]	niet gevonden	22	26	-	MD **8.1 lager** (9.63 lager tot 6.57 lager)	⨁◯◯◯ ZEER LAAG	NIET BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Single study; impossible to grade for inconsistency
b. Downgraded by 2; population is highly specific (veteran men exposed to sulfur-mustard gas), measurement tool used to score pruritus is unvalidated
c. Downgraded by 1; optimal information size not reached

Auteur(s): Shohrati et al 2007
Vraagstelling: Hydroxyzine versus Doxepin voor Pruritus from SM exposure

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Hydroxyzine	Doxepin	Relatief (95% CI)	Absoluut (95% CI)		
Pruritus from SM exposure - Hydroxyzine vs Doxepin - Pruritus score 8 weeks (follow up: 8 weken; Scale from: 0 tot 48)												
1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	zeer ernstig [b]	ernstig [c]	niet gevonden	22	21	-	MD **1.1 hoger** (0.34 lager tot 2.54 hoger)	⨁◯◯◯ ZEER LAAG	NIET BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Single study; impossible to grade for inconsistency
b. Downgraded by 2; population is highly specific (veteran men exposed to sulfur-mustard gas), measurement tool used to score pruritus is unvalidated
c. Downgraded by 1; optimal information size not reached

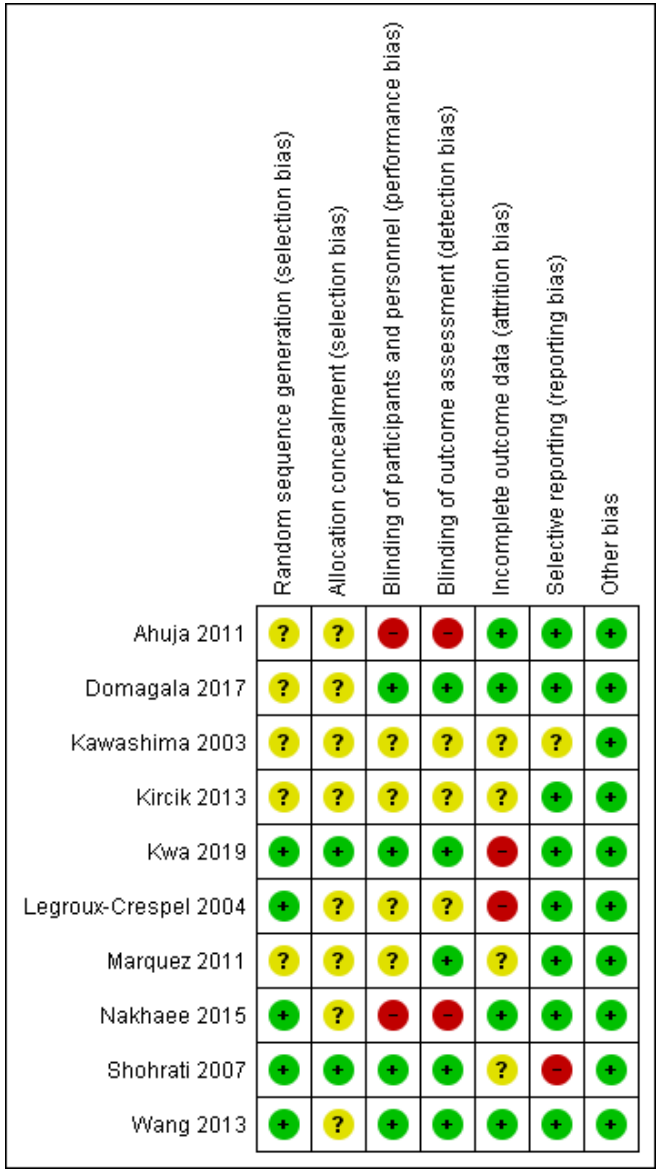
Auteur(s): Shohrati et al 2007
Vraagstelling: Cetirizine versus Doxepin voor Pruritus from SM exposure

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Cetirizine	Doxepin	Relatief (95% CI)	Absoluut (95% CI)		
Pruritus from SM exposure - Cetirizine vs Doxepin - Pruritus score 8 weeks (follow up: 8 weken; Scale from: 0 tot 48)												
1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	zeer ernstig [b]	ernstig [c]	niet gevonden	26	21	-	MD **7 lager** (8.6 lager tot 5.4 lager)	⨁◯◯◯ ZEER LAAG	NIET BELANGRIJK

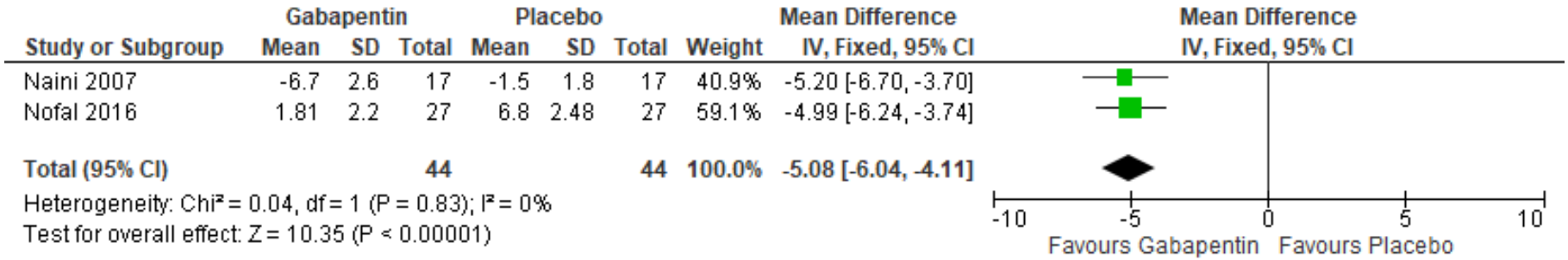
CI: Confidence interval; **MD:** Mean difference

Explanations
a. Single study; impossible to grade for inconsistency
b. Downgraded by 2; population is highly specific (veteran men exposed to sulfur-mustard gas), measurement tool used to score pruritus is unvalidated
c. Downgraded by 1; optimal information size not reached

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

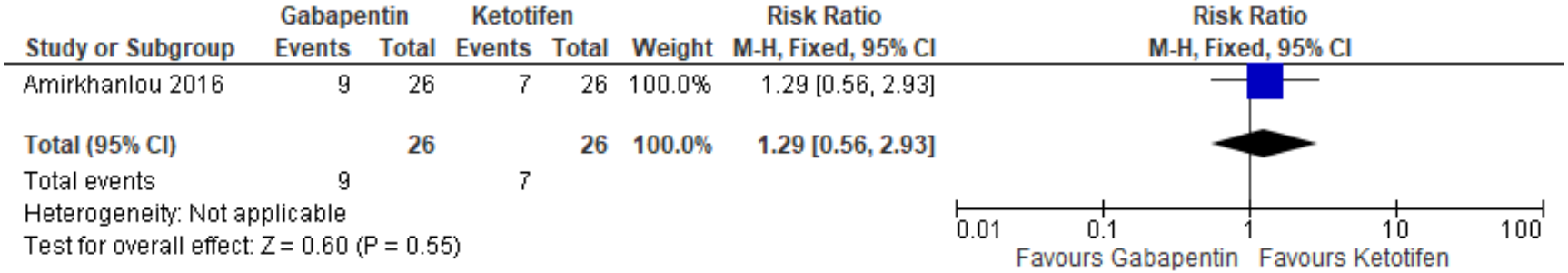


Gabapentine (2020): Meta-analyse

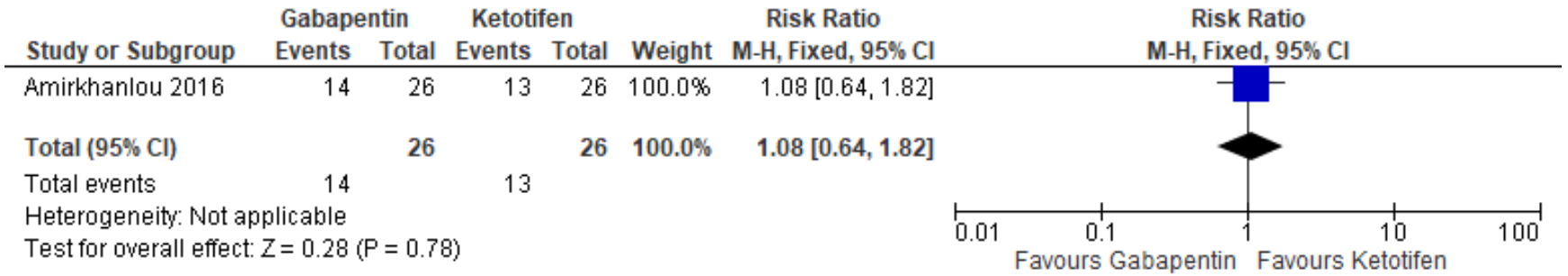


Forest plot of comparison: Uremic pruritus - Gabapentin vs Placebo - VAS, outcome: VAS 4 weeks.

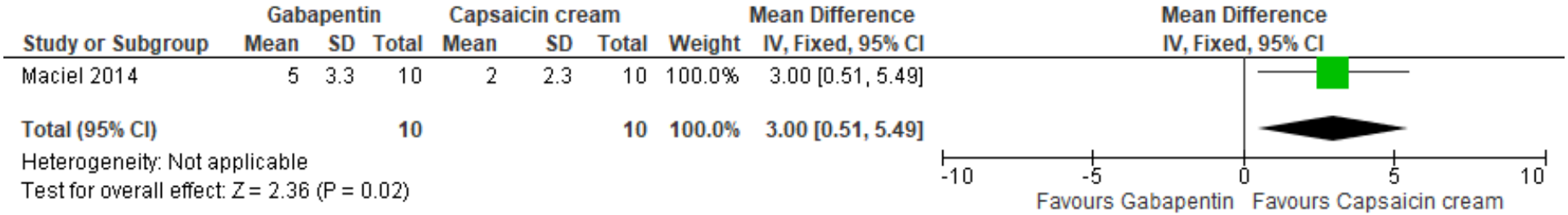
Forest plot of comparison: Uremic pruritus - Gabapentin vs Pregabalin - VAS, outcome: VAS 14 weeks.



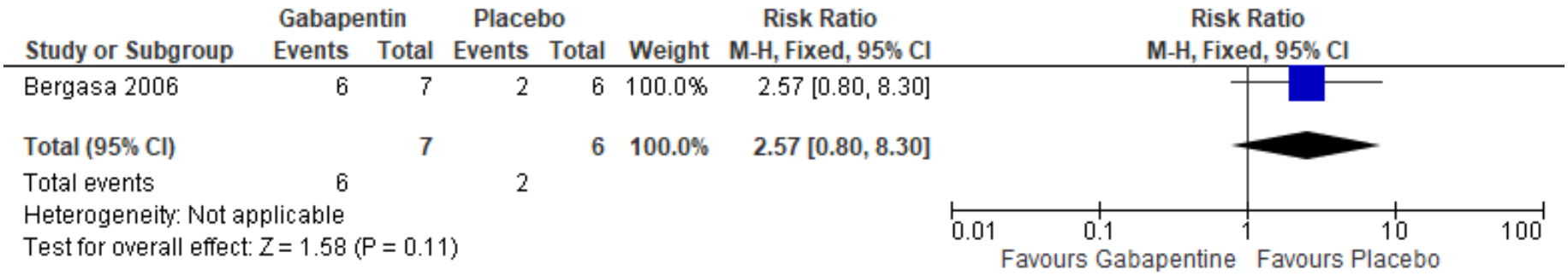
Forest plot of comparison: Uremic pruritus - Gabapentin vs Ketotifen - Response to treatment, outcome: Partial response to treatment.



Forest plot of comparison: Uremic pruritus - Gabapentin vs Ketotifen - Response to treatment, outcome: Complete response to treatment.



Forest plot of comparison: Notalgia paresthetica - Gabapentin vs Capsaicin cream - outcome: VAS 4 weeks.



Forest plot of comparison: 5 Cholestatic pruritus - Gabapentin vs Placebo - outcome: 1 or more adverse events.

GRADE Summary of Findings (SoF) tabellen Gabapentin

Auteur(s): Naini et al 2007, Nofal et al 2016
Vraagstelling: Gabapentin versus Placebo voor uremic pruritus

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Gabapentin	Placebo	Relatief (95% CI)	Absoluut (95% CI)		
Gabapentin vs Placebo - VAS 4 weeks (Scale from: 0 tot 10)												
2	gerandomiseerde trials	ernstig [a]	niet ernstig	niet ernstig	ernstig [b]	niet gevonden	44	44	-	MD **5.08 lager** (6.04 lager tot 4.11 lager)	⊕⊕◯◯ LAAG	CRUCIAAL

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Downgraded by 1; Nofal 2016 was a single-blinded trial, Naini 2007 had insufficient information provided to assess random selection bias (including allocation concealment) and detection bias.
b. Downgraded by 1; low amount of events under the Optimal Information Size for both studies

Auteur(s): Solak 2012
Vraagstelling: Gabapentin versus Pregabalin voor uremic pruritus

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Gabapentin	Pregabalin	Relatief (95% CI)	Absoluut (95% CI)		
Uremic pruritus - Gabapentin vs Pregabalin - VAS 14 weeks (Scale from: 0 tot 10)												
1	gerandomiseerde trials	zeer ernstig [a]	niet ernstig [b]	ernstig	ernstig [c]	niet gevonden	25	25	-	MD **0.02 hoger** (1.06 lager tot 1.1 hoger)	⨁◯◯◯ ZEER LAAG	BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

Explanations
a. Downgraded by 2; Participants and outcome assessors were not blinded, high number of drop-outs without explanation of how the analysis was performed.
b. Single study; impossible to grade for inconsistency
c. Downgraded by 1; optimal information size not reached.

Auteur(s): Amirkhanlou 2016
Vraagstelling: Gabapentin versus Ketotifen voor uremic pruritus

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Gabapentin	Ketotifen	Relatief (95% CI)	Absoluut (95% CI)		
Uremic pruritus - Gabapentin vs Ketotifen - Complete response to treatment (follow up: 2 weken)												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Gabapentin	Ketotifen	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	ernstig	zeer ernstig [b]	niet gevonden	14/26 (53.8%)	13/26 (50.0%)	**RR 1.08** (0.64 tot 1.82)	**40 meer per 1.000** (from 180 minder tot 410 meer)	⨁◯◯◯ ZEER LAAG	NIET BELANGRIJK
Uremic pruritus - Gabapentin vs Ketotifen - Partial response to treatment (follow up: 2 weken)												
1	gerandomiseerde trials	niet ernstig	niet ernstig [a]	ernstig	zeer ernstig [b]	niet gevonden	9/26 (34.6%)	7/26 (26.9%)	**RR 1.29** (0.56 tot 2.93)	**78 meer per 1.000** (from 118 minder tot 520 meer)	⨁◯◯◯ ZEER LAAG	NIET BELANGRIJK

CI: Confidence interval; **RR:** Risk ratio

Explanations
a. Single study; impossible to grade for inconsistency
b. Downgraded by 2; optimal information size not reached, CI crosses threshold of recommendation/non-recommendation.

Auteur(s): Maciel 2014
Vraagstelling: Gabapentin versus Capsaicin cream voor pruritus due to notalgia paresthetica

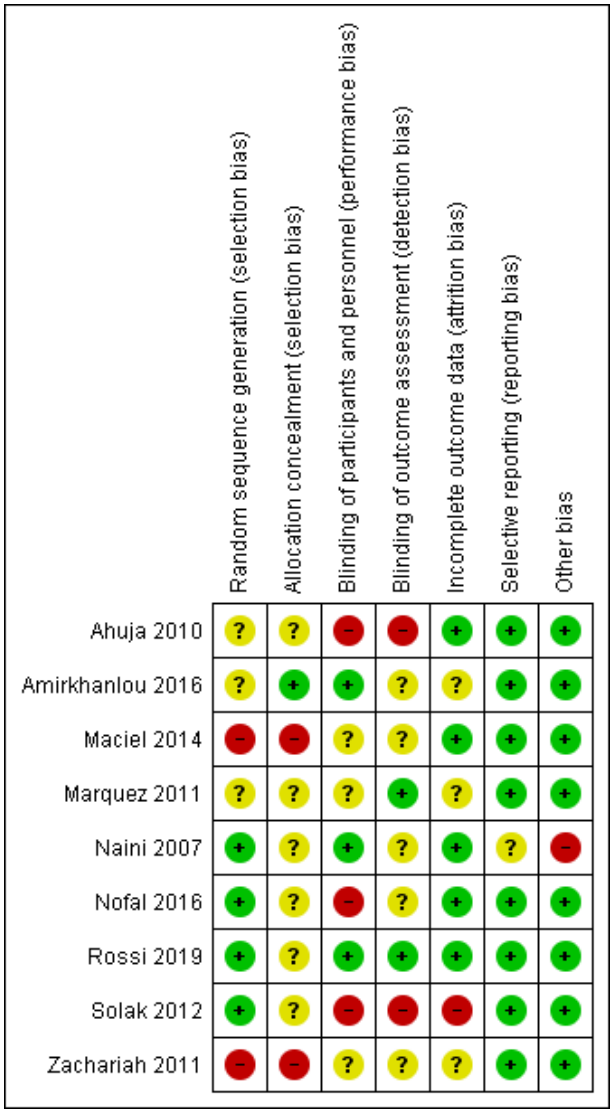
Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Gabapentin	Capsaicin cream	Relatief (95% CI)	Absoluut (95% CI)		
Pruritus from notalgia paresthetica - Gabapentin vs Capsaicin cream - VAS 4 weeks (follow up: 4 weken; Scale from: 0 tot 10)												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Gabapentin	Capsaicin cream	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	zeer ernstig [a]	niet ernstig [b]	zeer ernstig	ernstig [c]	niet gevonden	10	10	-	MD **3 hoger** (0.51 hoger tot 5.49 hoger)	⨁◯◯◯ ZEER LAAG	BELANGRIJK

CI: Confidence interval; **MD:** Mean difference

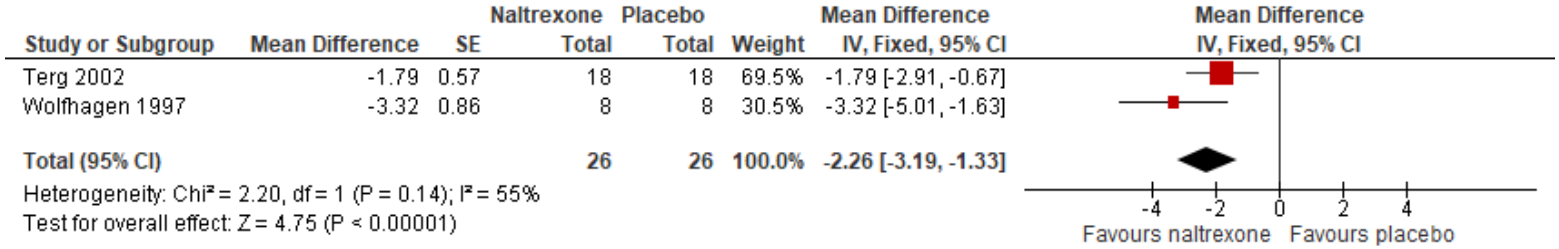
Explanations
a. Downgraded by 2; selection bias, lack of randomization
b. Single study; impossible to grade for inconsistency
c. Downgraded by 1; optimal information size not reached

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

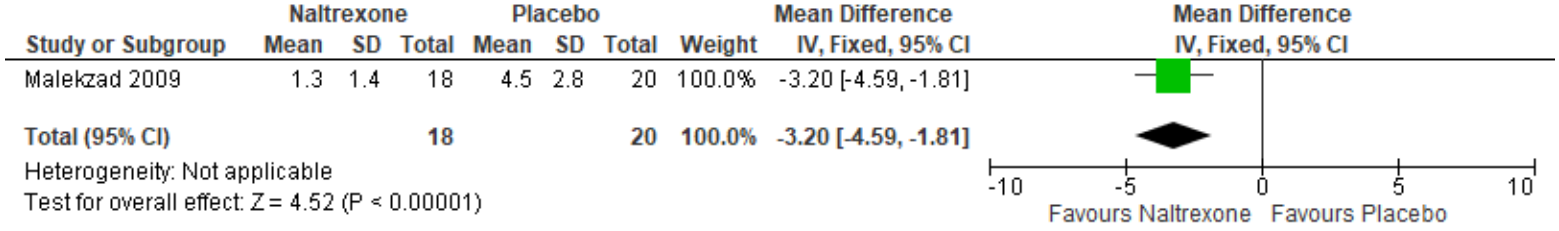


Naltrexone (2020): Meta-analyse

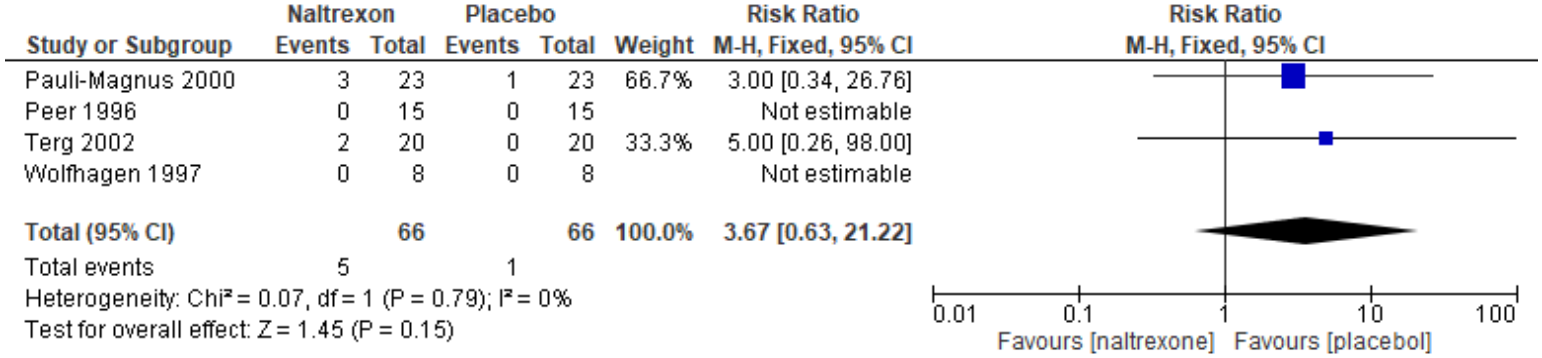
Forest plot of comparison: Naltrexone versus placebo, outcome: pruritus on VAS scale (0-10 cm) in CP participants;



Forest plot of comparison: Naltrexone versus placebo, outcome: pruritus on VAS scale (0-10cm) in AD patients;



Forest plot of comparison: Naltrexone versus placebo, outcome: risk of dropout due to adverse effect in patients with UP and CP;

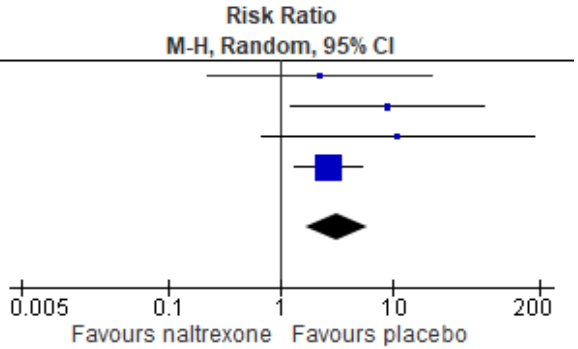


** Malekzad et al 2009 excluded; reason dropouts not mentioned*

Forest plot of comparison: Naltrexone versus placebo, outcome: risk for at least one adverse event per participant; UP, CP and AD patients;

Study or Subgroup	Naltrexone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Malekzad 2009	2	18	1	20	7.2%	2.22 [0.22, 22.49]
Pauli-Magnus 2000	9	23	1	23	9.8%	9.00 [1.24, 65.41]
Peer 1996	5	15	0	15	4.9%	11.00 [0.66, 182.87]
Terg 2002	16	20	6	20	78.0%	2.67 [1.32, 5.39]
Total (95% CI)		**76**		**78**	**100.0%**	**3.18 [1.71, 5.92]**
Total events	32		8			

Heterogeneity: Tau² = 0.00; Chi² = 2.51, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.64 (P = 0.0003)

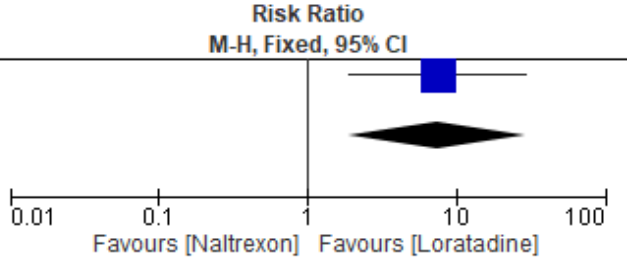


** Wolfhagen et al 1997 excluded; only total number of adverse effects reported and not per participant*

Forest plot of comparison: Naltrexone versus Loratadine, outcome: Risk for at least one adverse event per participant; UP patients

Study or Subgroup	Naltrexon Events	Total	Loratadine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Legroux-Crespel 2004	15	26	2	26	100.0%	7.50 [1.90, 29.56]
Total (95% CI)		**26**		**26**	**100.0%**	**7.50 [1.90, 29.56]**
Total events	15		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.88 (P = 0.004)



GRADE Summary of Findings (SoF) tabellen Naltrexone

Auteur(s):
Cholestatic pruritus: Wolfhagen et al 1997, Terg et al 2002
Uremic pruritus: Peer et al 1996, Pauli-Magnus et al 2000, Legroux-Crespel et al 2004 (Naltrexon versus Loratadine)
Atopic dermatitis: Malekzad 2009
Vraagstelling: Naltrexone versus placebo/loratadine in patients with atopic dermatitis, cholestatic pruritus or uremic pruritus (pruritus, risk for adverse effects and quality of life)

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Naltrexon	Placebo/Loratadine	Relatief (95% CI)	Absoluut (95% CI)		
Naltrexone versus placebo - decrease of pruritus in patients with cholestatic pruritus (follow up: range 2 weken tot 4 weken; vastgesteld met: 10 cm VAS)												
2	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	zeer ernstig [a]	niet gevonden	26	26	-	Mean difference **2.26 lager** (3.19 lager tot 1.33 lager)	⨁⨁◯◯ LAAG	CRUCIAAL
Naltrexone versus placebo - decrease of pruritus in patients with uremic pruritus (follow up: range 1 weken tot 4 weken; vastgesteld met: 10 cm VAS)												
2	gerandomiseerde trials	niet ernstig	zeer ernstig	niet ernstig	ernstig	niet gevonden	The results of Peer et al. and Pauli Magnus et al. regarding the effect of naltrexon in patients with uremic pruritus were contradictory. Peer et al. described a significant short-term efficacy of naltrexon compared to placebo. The results of Pauli Magnus et al. showed a non-significant difference between naltrexon and placebo treatment periods. Quality of evidence downgraded by two levels because of inconsistency (see above mentioned reason) and by one level because of imprecision; low number patients included.				⨁◯◯◯ ZEER LAAG	CRUCIAAL
Naltrexone versus placebo - decrease of pruritus in patients with atopic dermatitis (follow up: gemiddeld 2 weken; vastgesteld met: 10 cm VAS)												
1	gerandomiseerde trials	ernstig [b]	niet ernstig	niet ernstig	zeer ernstig [a]	niet gevonden	18	20	-	Niet gepoold	⨁◯◯◯ ZEER LAAG	CRUCIAAL
Naltrexone versus placebo - risk for at least one adverse event per participant; patients with atopic dermatitis, cholestatic pruritus and uremic pruritus (follow up: range 1 weken tot 4)												
4 [c]	gerandomiseerde trials	niet ernstig [d]	niet ernstig	niet ernstig	ernstig [e]	niet gevonden	32/76 (42.1%)	8/78 (10.3%)	**RR 3.18** (1.71 tot 5.92)	**224 meer per 1.000** (van 73 meer tot 505 meer)	⨁⨁⨁◯ REDELIJK	CRUCIAAL
Naltrexone versus placebo - risk for dropout due to adverse effect(s); patients with atopic dermatitis, cholestatic pruritus and uremic pruritus (follow up: range 1 weken tot 4 weken)												

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Naltrexon	Placebo/Loratadine	Relatief (95% CI)	Absoluut (95% CI)		
4 [f]	gerandomiseerde trials	niet ernstig	niet ernstig	niet ernstig	zeer ernstig [g]	niet gevonden	5/66 (7.6%)	1/66 (1.5%)	**RR 3.67** (0.63 tot 21.22)	**40 meer per 1.000** (van 6 minder tot 306 meer)	⨁⨁◯◯ LAAG	CRUCIAAL

Naltrexone versus Loratadine - risk for at least one adverse event per participant; patients with uremic pruritus (follow up: gemiddeld 2 weken)

1	gerandomiseerde trials	zeer ernstig [h]	niet ernstig	niet ernstig	zeer ernstig [a]	niet gevonden	15/26 (57.7%)	2/26 (7.7%)	**RR 7.50** (1.90 tot 29.56)	**500 meer per 1.000** (van 69 meer tot 1.000 meer)	⨁◯◯◯ ZEER LAAG	CRUCIAAL

Naltrexone versus placebo - Quality of life in patients with cholestatic or uremic pruritus - niet gemeten

-	-	-	-	-	-	-	-	-	-	-	-	CRUCIAAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Quality of evidence downgraded by two levels because of imprecision: very low number patients included
b. Quality of evidence downgrade by one level due to risk of bias: high risk of attrition and reporting bias
c. Wolfhagen et al 1997 excluded; only total number of adverse effects reported and not per participant
d. Quality of evidence not downgraded despite high risk of bias in Malekzad 2009 due to low weight of this study
e. Quality of evidence downgraded by one level because of imprecision: wide CI 95% interval
f. Malekzad et al 2009 excluded; reason dropouts not mentioned
g. Quality of evidence downgraded by two levels because of imprecision: low number patients included and wide CI 95% interval
h. Quality of evidence downgraded by two levels due to risk of bias: high risk of performance bias, detection bias, attrition bias and selective reporting bias

GRADE Summary of Findings (SoF) tabellen Psychological treatment

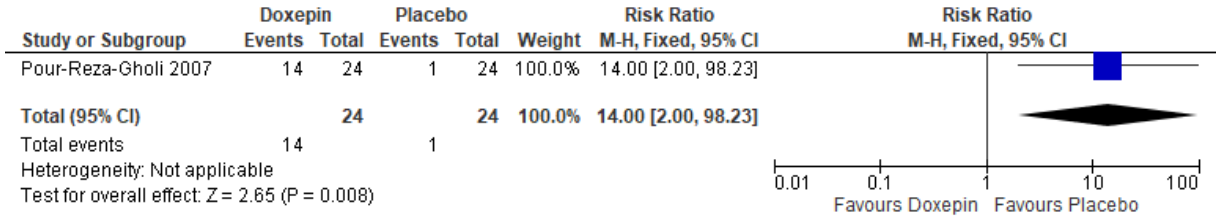
Vraagstelling: Psychological treatment + standard medical care (SMC) versus SMC voor Chronic pruritus
Setting:
Literatuur: Van Os-Medendorp 2007

Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Psychological treatment	Standard medical care	Relatief (95% CI)	Absoluut (95% CI)		
Psychological treatment + standard medical care(SMC) vs SMC - outcome: N with high intensity of itching and scratching (follow up: 3 maanden)												
1	gerandomiseerde trials	zeer ernstig [a]	niet ernstig [b]	ernstig [c]	zeer ernstig [d]	niet gevonden	14/25 (56.0%)	19/32 (59.4%)	**RR 0.94** (0.60 tot 1.48)	**36 minder per 1.000** (from 238 minder tot 285 meer)	⊕◯◯◯ ZEER LAAG	NOT IMPORTANT
Psychological treatment + standard medical care(SMC) vs SMC - outcome: N with high intensity of itching and scratching (follow up: 9 maanden)												
1	gerandomiseerde trials	zeer ernstig [a]	niet ernstig [b]	zeer ernstig [c]	zeer ernstig [d]	niet gevonden	12/24 (50.0%)	16/29 (55.2%)	**RR 0.91** (0.54 tot 1.52)	**50 minder per 1.000** (from 254 minder tot 287 meer)	⊕◯◯◯ ZEER LAAG	NOT IMPORTANT
Psychological treatment + standard medical care(SMC) vs SMC - outcome: impact on Quality of Life (follow up: 3 maanden)												
1	gerandomiseerde trials	zeer ernstig [a]	niet ernstig [b]	ernstig [e]	zeer ernstig [d]	niet gevonden	29	37	-	MD **0.09 hoger** (2.39 lager tot 2.57 hoger)	⊕◯◯◯ ZEER LAAG	NIET BELANGRIJK
Psychological treatment + standard medical care(SMC) vs SMC - outcome: impact on Quality of Life (follow up: 9 maanden)												
1	gerandomiseerde trials	zeer ernstig [a]	niet ernstig [b]	ernstig [e]	zeer ernstig [d]	niet gevonden	23	30	-	MD **0.42 SD hoger** (2.28 lager tot 3.12 hoger)	⊕◯◯◯ ZEER LAAG	NIET BELANGRIJK

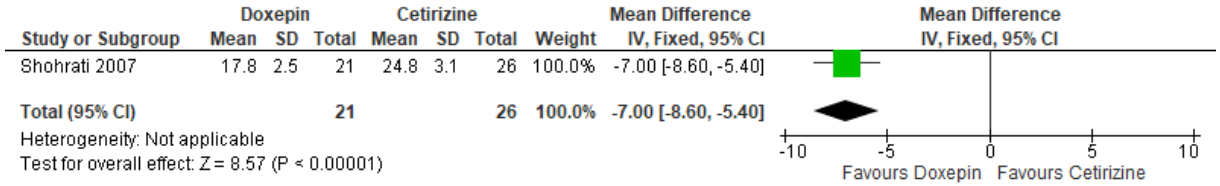
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations
a. Incomplete outcome data at follow-up (loss-of-follow up?), allocation concealment not possible (1 group had appointments with the nursing programme, the other only standard medical care)
b. Single study; impossible to grade inconsistency
c. The outcome was not reported in the visual analogue scale for itch. It is reported as the combined number of patients with high intensity of itching and high intensity of scratching. Population includes patients with pruritus due to dermatological diseases.
d. Optimal information size not reached, C.I. passes clinical decision threshold between recommending and not recommending
e. Population includes patients with pruritus due to dermatological diseases.

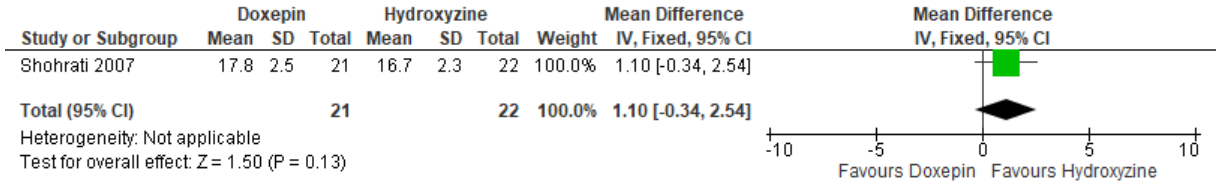
Tricyclische antidepressiva (2020): Meta-analyse



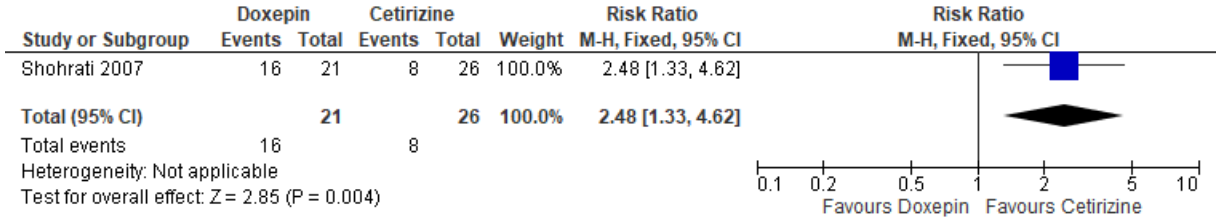
Forest plot of comparison: 1 Doxepin vs Placebo, outcome: 1.1 Complete improvement of pruritus.



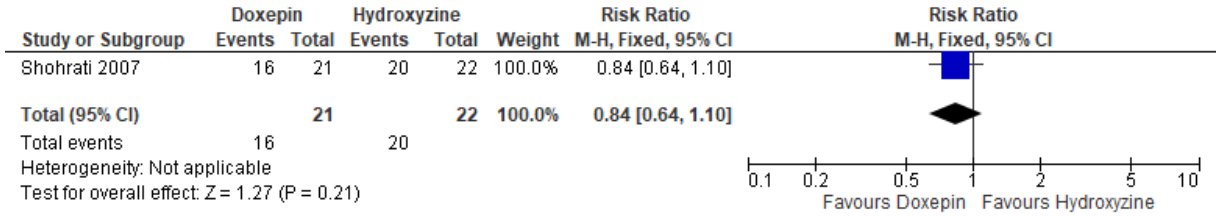
Forest plot of comparison: 1 Doxepin vs Cetirizine, outcome: 1.2 Pruritus calculated score.



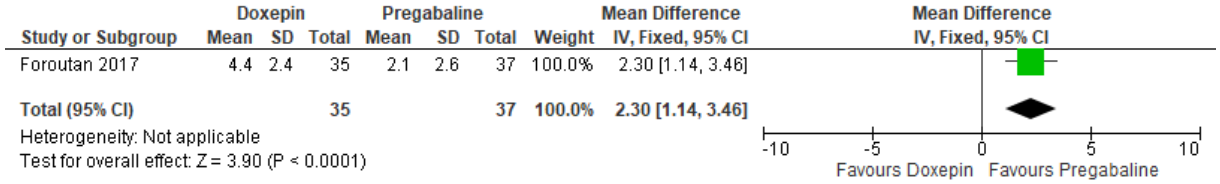
Forest plot of comparison: 1 Doxepin vs Hydroxyzine, outcome: 1.3 Pruritus calculated score



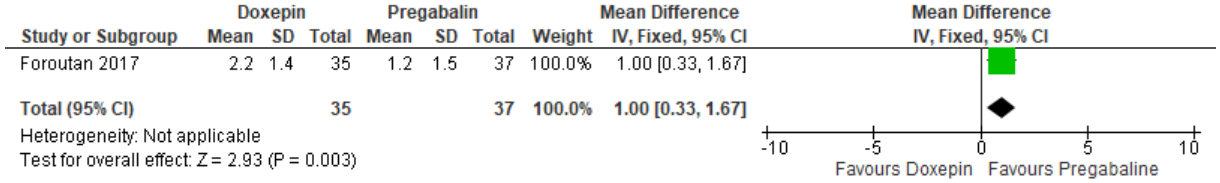
Forest plot of comparison: 1 Doxepin vs Cetirizine, outcome: 1.4 1 >= adverse event.



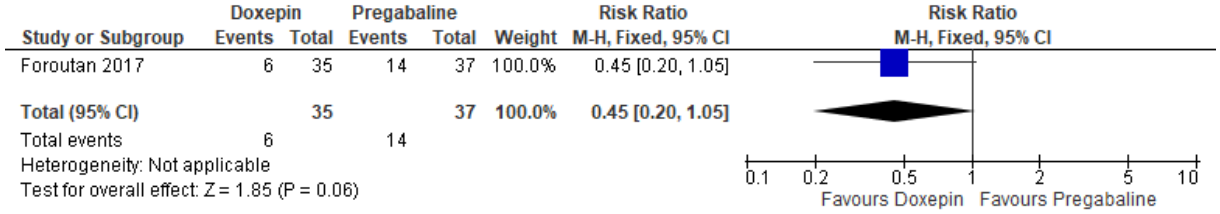
Forest plot of comparison: 1 Doxepin vs Hydroxyzine, outcome: 1.4 1 >= adverse event.



Forest plot of comparison: 1 Doxepin vs Pregabaline, outcome: 1.5 VAS.



Forest plot of comparison: 1 Doxepin vs Pregabaline, outcome: 1.6 DLQI.



Forest plot of comparison: 1 Doxepin vs Pregabaline, outcome: 1.7 1 or more adverse effects.

GRADE Summary of Findings (SoF) tabellen Tricyclische antidepressiva

Auteur(s): Pour-Reza-Gholi et al 2007, Foroutan et al 2017, Shohrati et al 2006
Vraagstelling: Doxepin versus Placebo / Pregabaline voor Chronic pruritus

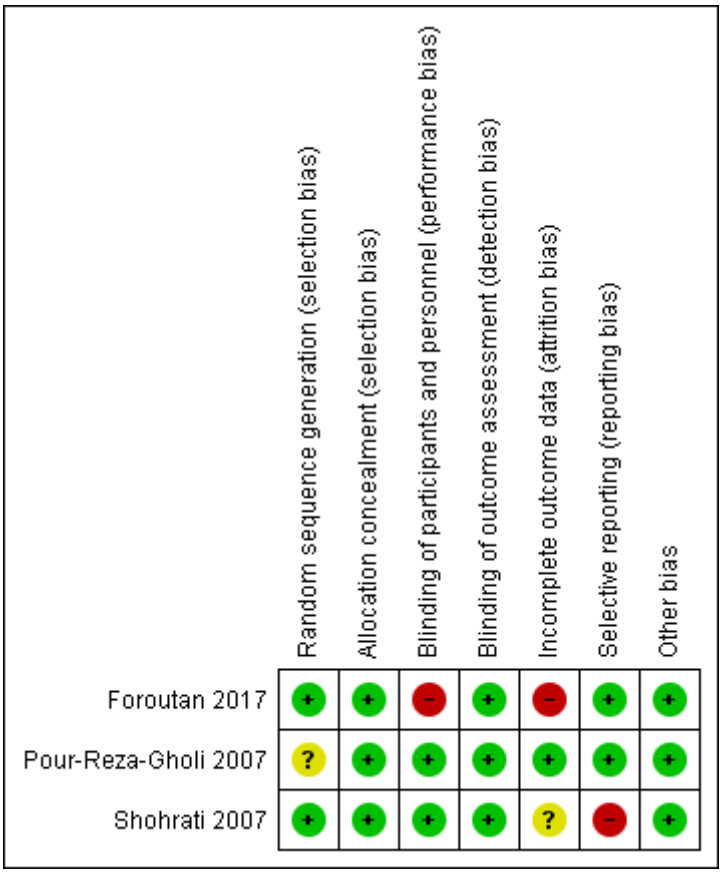
Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Doxepin	Placebo / Pregabaline	Relatief (95% CI)	Absoluut (95% CI)		
Doxepin vs Pregabaline - VAS (vastgesteld met: VAS score (0-10); Scale from: 0 tot 10)												
1	gerandomiseerde trials	ernstig [a]	niet ernstig	ernstig [b]	ernstig [c]	niet gevonden	35	37	-	MD **2.3 hoger** (1.14 hoger tot 3.46 hoger)	⨁◯◯◯ ZEER LAAG	
Doxepin vs Pregabaline - Dermatology Life Quality Index (vastgesteld met: Questionnaire; Scale from: 0 tot 30)												
1	gerandomiseerde trials	ernstig [a]	niet ernstig	ernstig [b]	ernstig [c]	niet gevonden	44	46	-	MD **1 hoger** (0.33 hoger tot 1.67 hoger)	⨁◯◯◯ ZEER LAAG	
Doxepin vs Pregabaline - Having 1 or more adverse effects												
1	gerandomiseerde trials	ernstig [a]	niet ernstig [d]	zeer ernstig [e]	zeer ernstig [c]	niet gevonden	6/35 (17.1%)	14/37 (37.8%)	**RR 0.45** (0.20 tot 1.05)	**208 minder per 1.000** (from 303 minder tot 19 meer)	⨁◯◯◯ ZEER LAAG	
Doxepin vs Placebo - Pruritus improvement (vastgesteld met: Subjective assessment by questioning participants; Scale from: 0 tot 2)												

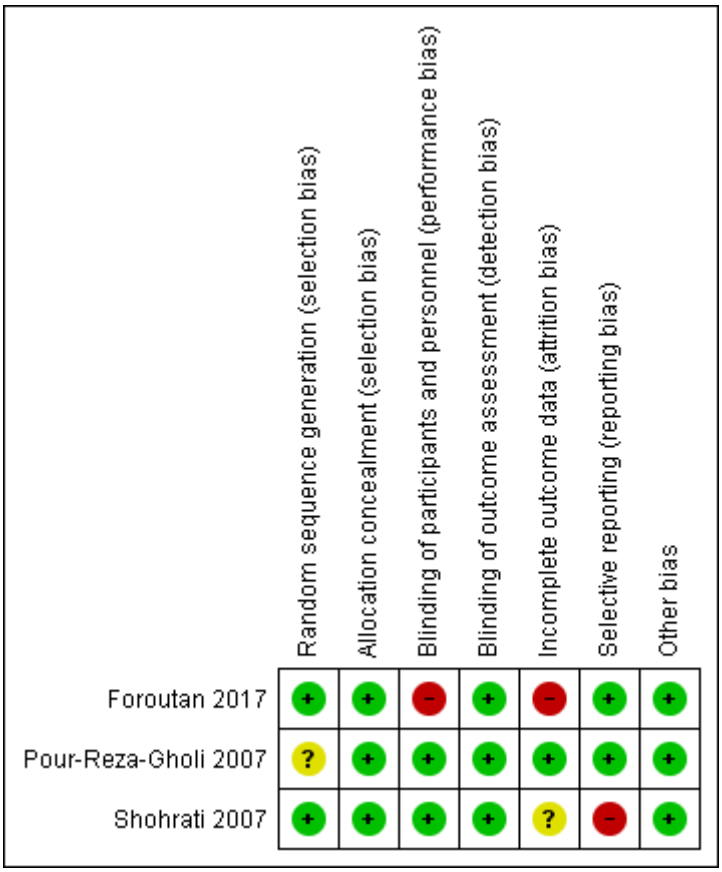
Certainty assessment							Aantal patiënten		Effect		Certainty	Importantie
Aantal studies	Studieopzet	Risk of bias	Inconsistentie	Indirect bewijs	Onnauwkeurigheid	Andere factoren	Doxepin	Placebo / Pregabaline	Relatief (95% CI)	Absoluut (95% CI)		
1	gerandomiseerde trials	niet ernstig	niet ernstig	ernstig	ernstig [c]	niet gevonden	24	24	-	RR **14 meer** (2 meer tot 98.23 meer)	⨁⨁◯◯ LAAG	
Doxepin vs Cetirizine - Pruritus calculated score (Scale from: 0 tot 48)												
1	gerandomiseerde trials	niet ernstig	niet ernstig [d]	zeer ernstig [f]	ernstig [g]	niet gevonden	21	26	-	MD **7 lager** (8.6 lager tot 5.4 lager)	⨁◯◯◯ ZEER LAAG	
Doxepin vs Hydroxyzine - Pruritus calculated score (Scale from: 0 tot 48)												
1	gerandomiseerde trials	niet ernstig	niet ernstig [d]	zeer ernstig [f]	ernstig [g]	niet gevonden	21	22	-	MD **1.1 hoger** (0.34 lager tot 2.54 hoger)	⨁◯◯◯ ZEER LAAG	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations
a. high risk of performance bias due to patients not being blinded to intervention (single-blinded study) and high risk of attrition bias due to high percentage of loss-of-follow up (>20%)
b. indirect comparison with different group (not placebo)
c. low sample size (less than the optimal information size)
d. Single study; impossible to grade for inconsistency
e. Downgraded by 2; varying doses of medication in both groups, method of comparison is not placebo
f. Downgraded by 2; population and comparison is indirect, measurement tool is invalid
g. Downgraded by 1; optimal information size not reached

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Foroutan 2017
Pour-Reza-Gholi 2007
Shohrati 2007

Bijlage 8: Kennislacunes

Bij de modulaire herziening van de richtlijn Chronische Jeuk (2022) is geconstateerd dat er een aantal vragen resteren die niet beantwoord kunnen worden, omdat er onvoldoende bewijs beschikbaar is. Deze lacunes zijn in onderstaand overzicht weergegeven:

- Meer algemeen wetenschappelijk onderzoek naar de systemische middelen voor de behandeling van chronische jeuk.
- ‘Hoe ouder hoe meer last van jeuk’. Meer onderzoek naar de pathogenese en therapie van jeuk op oudere leeftijd.
- Is de behandeling van jeuk op jonge leeftijd ook gewoon toe te passen op oudere leeftijd?

Bijlage 9: Implementatieplan

Inleiding
Ten behoeve van de implementatie van de *Richtlijn Chronische Jeuk* heeft de NVDV c.q. de werkgroep een inventarisatie gedaan naar de eventuele bevorderende en belemmerende factoren voor het naleven van de aanbevelingen. Daarbij is er advies uitgebracht over het tijdspad voor implementatie, de daarvoor benodigde randvoorwaarden en de acties die door verschillende partijen ondernomen dienen te worden.

Werkwijze

Om tot dit plan te komen heeft de werkgroep per aanbeveling in de richtlijn nagedacht over:

- Per wanneer de aanbeveling overal geïmplementeerd moet zijn;
- De verwachtte impact van implementatie van de aanbeveling op de zorgkosten;
- Randvoorwaarden om de aanbeveling te kunnen implementeren;
- Mogelijk barrières om de aanbeveling te kunnen implementeren;
- Mogelijke acties om de implementatie van de aanbeveling te bevorderen;
- De verantwoordelijke partij voor de te ondernemen acties.

Lezers van dit implementatieplan dienen rekening te houden met dat er verschillen zijn tussen ‘sterke aanbevelingen’ en ‘zwakke aanbevelingen’. In het eerste geval doet de richtlijncommissie een duidelijke uitspraak over iets dat wel of niet gedaan moet worden. In het tweede geval wordt de aanbeveling minder zeker gesteld en spreekt de werkgroep haar voorkeur of advies uit, maar laat zij meer ruimte voor alternatieven. Een reden hiervoor is bijvoorbeeld dat er onvoldoende wetenschappelijk bewijs is om de aanbeveling te onderbouwen. Een zwakke aanbeveling is te herkennen aan de formulering en begint bijvoorbeeld met ‘Overweeg om…’. Zowel voor de sterke als voor de zwakke aanbevelingen heeft de werkgroep nagedacht over de implementatie. Alleen voor sterk geformuleerde aanbevelingen worden implementatietermijnen gegeven.

Implementatietermijnen
Jeuk is nog voor vele onbekend terrein. Het duidelijk maken van de ontstaanswijze van de verschillende vormen van jeuk is de belangrijkste stap in het implementatieplan. Jeuk heeft in de meeste gevallen een neuro-immunologisch oorzaak en moet al zodanig behandeld worden. Voorzichtigheid is geboden in de verschillende subgroepen zoals, ouderen, kinderen en zwangeren.

Voor de volgende aanbevelingen geldt dat zij zo spoedig mogelijk overal nageleefd dienen te worden. In de meeste gevallen betekent dat dat de aanbevelingen binnen een jaar na het uitbrengen van de richtlijn geïmplementeerd moet zijn. Dit geldt voor de volgende aanbevelingen:

Aanbeveling	**Toelichting**
Capsaïcine crème	Capsaïcine in crème of pleisters in doseringen van 0,025% tot 0,075% is aan te bevelen bij notalgia paresthetica.
UVB-therapie	Indien maximale lokale behandeling én systemische behandeling met antihistaminica, een neurolepticum of antidepressivum ineffectief (of gecontraïndiceerd) is, kan bij patiënten met CPUO met smalspectrum UVB-therapie worden gestart. Ook toe te passen bij patiënten met uremische pruritus.
Systemische glucocorticosteroiden	Systemische glucocorticosteroiden kunnen als

	korte termijn (inductie) behandeling van refractaire chronische jeuk worden ingezet. Een kortdurende predniso(lo)n-kuur kan helpen inventariseren of de chronische jeuk reageert op anti-inflammatoire behandeling. Ciclosporine, methotrexaat en azathioprine kunnen uitsluitend ingezet worden bij CPUO op grond van de expertise van de behandelend specialist.
Tricyclische antidepressiva (TCA's)	TCA's nortriptyline, amitriptyline en het tetracyclische antidepressivum mirtazapine komen in aanmerking bij refractaire CPUO; in het bijzonder bij psychogene, paraneoplastische en uremische jeuk. Overweeg hierbij ook psychologische ondersteuning.

Voor sommige aanbevelingen geldt echter dat zij niet direct overal kunnen worden ingevoerd, bijvoorbeeld vanwege een gebrek aan middelen, expertise of de juiste organisatievormen. In sommige gevallen dient ook rekening te worden gehouden met een leercurve. Daarnaast kan de aanwezigheid van personeel of faciliteiten of de afstemming tussen professionals een belemmering zijn om de aanbevelingen op korte termijn in te voeren.
Voor de volgende aanbevelingen geldt daarom een implementatietermijn van één tot drie jaar:

Aanbeveling	**Toelichting**
Neurokinine-1-receptorantagonisten	Aprepitant kan worden overwogen bij patiënten met refractaire CPUO.

Impact op zorgkosten

Veel aanbevelingen brengen geen of nauwelijks gevolgen met zich mee voor de zorgkosten. Een aantal aanbevelingen doet dit echter wel. In onderstaande tabel wordt per module beschreven welke aanbevelingen volgens de richtlijncommissie een belangrijk effect met zich meebrengen op de zorgkosten en welk effect dit is.

Aanbeveling	**Toelichting**
Geen	**-**

Implementatie van de richtlijn in dagelijkse praktijkvoering

Richtlijnen die ontwikkeld en verspreid zijn, vinden niet vanzelf hun weg in de dagelijkse praktijk. Het enkel verspreiden van de richtlijn (disseminatie) volstaat over het algemeen niet om daadwerkelijke toepassing in de dagelijkse praktijk te garanderen.
Een systematische aanpak en gerichte (implementatie) activiteiten zijn meestal noodzakelijk om daadwerkelijk gebruik in de praktijk te waarborgen.
Vanuit de NVDV toetst de visitatiecommissie op de norm: 'werken volgens richtlijnen'. Dit om de implementatie van richtlijnen in de dagelijkse praktijk te bevorderen.
Hieronder worden aanbevelingen gedaan die op lokaal niveau door vakgroepen, maatschappen of praktijken (i.c. dermatologen, huisartsen, huidtherapeuten en huidverpleegkundigen) kunnen worden opgepakt om te bevorderen dat de richtlijn op locatie succesvol wordt geïmplementeerd.

- Stel binnen uw vakgroep, maatschap of praktijk een persoon aan die verantwoordelijk is voor het bekend maken, implementeren en evalueren van het gebruik van de richtlijn.
- Bespreek wat de aanbevelingen uit de richtlijn voor uw vakgroep, maatschap of praktijk betekenen: Verken en bespreek welke aspecten van de zorg voor verbetering in

aanmerking komen dan wel welke lokale factoren het al dan niet opvolgen van aanbevelingen in de praktijk beïnvloeden.
- Vertaal en/of incorporeer specifieke aanbevelingen uit de richtlijn in lokale protocollen, procedures en/of afspraken.
- Vergemakkelijk het raadplegen of het vinden van de richtlijn door deze bijvoorbeeld toegankelijk te maken via kwaliteitsportaal in het ZIS of door te linken naar de NVDV database/website en/of de landelijke richtlijnendatabase (www.richtlijnendatabase.nl).
- Bespreek de richtlijn tijdens refereerbijeenkomsten, opleidingsbesprekingen en complicatiebesprekingen.
- Verwijs tijdens besprekingen naar de aanbevelingen in de richtlijn bij daartoe geëigende casuïstiek.
- Stimuleer het gebruik/raadplegen van richtlijnen bij alle leden van de vakgroep, maatschap of praktijk.

Initiatief nemende wetenschappelijke vereniging (NVDV)
• bekend maken van de richtlijn onder de andere betrokken wetenschappelijke – en beroepsverenigingen.

Alle direct betrokken wetenschappelijk verenigingen/beroepsorganisaties bekend maken van de richtlijn onder de leden;

• publiciteit voor de richtlijn maken door over de richtlijn te publiceren in tijdschriften en te vertellen op congressen;
• verzorgen van (bij)scholing en training om ervoor te zorgen dat de gewenste expertise geleverd kan worden voor het naleven van de richtlijn;
• controleren van de toepassing van de aanbevelingen middels audits en de kwaliteitsvisitatie;

De systeemstakeholders (onder andere zorgverzekeraars, NZA, (koepelorganisaties van) ziekenhuisbestuurders)
Van zorgverzekeraars wordt verwacht dat zij ter mede toezien op implementatie van de zorg die in deze richtlijn wordt aanbevolen. Over het algemeen is het waarschijnlijk dat noodzakelijke investeringen voor de baat uit gaan. De ‘sterk geformuleerde aanbevelingen’ in deze richtlijn kunnen, na verloop van de aangegeven implementatietermijnen door zorgverzekeraars worden gebruikt voor de inkoop van zorg.

Wetenschappers en subsidieverstrekkers

Onderzoek initiëren naar de kennislacunes.

Het Kennisinstituut van Medisch Specialisten
Toevoegen van richtlijn aan richtlijnendatabase. Opnemen van dit implementatieplan op een voor alle partijen goed te vinden plaats.