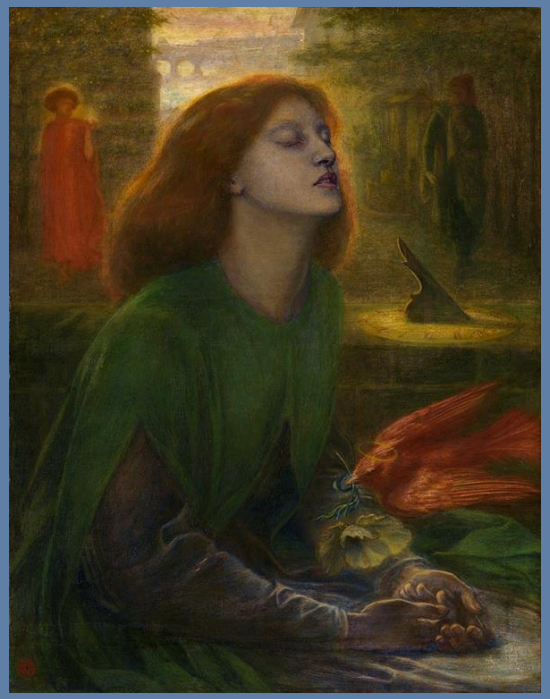

Dante Gabriel Rossetti - Beata Beatrix, 1863

MCH **DIGEST**
WETENSCHAPPELIJKE TIJDINGEN

Een maandelijkse wandeling door de medische literatuur

verschijnt maandelijks – **Juni 2024**

nr. **399**

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Nascholingsprogramma academiejaar 2023-2024

Webinars

- **WERKGROEP HUISARTSEN NASCHOLINGSCYCLUS, VERANTWOORDELIJKE PROF. DR. BIRGITTE SCHOENMAKERS**
- **DERDE DONDERDAG VAN DE MAAND**
- **AANVANG: 20.00U**

20.06.2024 Titel: Chronisch longlijden en COPD
Spreker: dr. Nikolaas De Maeyer
Moderator: dr. Evelien Lenaerts

Fysieke nascholingen

- **WERKGROEP HUISARTSEN MIDDAGNASCHOLING MCH**
- **TWEEDE DINSDAG VAN DE MAAND**
- **LOCATIE: SYNTRA LEUVEN**
- **AANVANG: 12.00U**

11.06.2024 Titel: Transmurale communicatie en samenwerking tussen ziekenhuizen, huisartsen en thuisverpleegkundigen
Spreker: dhr. Joris Paesen, EPD Consultant nexuzhealth
Moderator: dr. Jacqueline Van de Walle

P.U.K. – Druivenstreek vzw

- **VIERDE DONDERDAG VAN DE MAAND, VERANTWOORDELIJKE DR. NOËL MORTIER**
- **LOCATIE: MCH WEZEMBEEK-OPPEM**
- **AANVANG: 21.00U. STIPT**

27.06.2024 Titel: Kleine heelkunde: de kleine en praktische geheimpjes
Sprekers: dr. Thomas Douchy
Moderator: dr. Guido Istas

Verbazende inzichten

De twee laatste eeuwen is de gemiddelde levensduur zowat verdubbeld. De geneeskunde heeft daar toe bijgedragen, maar eveneens geleerden, activisten en ja zelfs het toeval. Het rariteitenkabinet van artsen die ooit zonder verpinken uitpakten met arsenicum, kwikderivaten, radioactief water, cocaïne en bloedzuigers is weg. Maar toch niet zolang geleden. Van waar de stroomversnelling?

De vooruitgang van de gezondheidszorg hebben we in het begin vooral te danken aan een kleurrijke stoet mensen van divers pluimage. En aan een open geest, nieuwsgierigheid en bereidheid tot risico's.

De uitroeiing van de pokken is een mooi voorbeeld. Wie weet dat de vaccinatie tegen pokken zijn wortels heeft in donker Afrika? Een predikant in Boston had een slaaf die de kennis van de variolatie van zijn stam had meegebracht. Afrikanen brachten een huidsnede toe en wreven ze in met etter uit pokkenletsels. Twee procent overleed er wel aan. Maar het beschermde wel wie de echte pokken kreeg, met een sterftecijfer van dertig procent. Toen in Boston een pokkenepidemie uitbrak paste onze predikant deze methode toe bij wie wilde. Met succes. Je zou er natuurlijk niet moeten mee afkomen op Kind en Gezin.

Een avontuurlijke Britse lady leerde de variolatie in Turkije kennen. Turken pasten het ook al lang toe. Ze aarzelde niet haar opinie daarover te verspreiden in Londen, dat ook werd geteisterd door de pokken. Haar relaties met het hof hielpen daarbij, zeker toen twee prinsessen werden gevarioleerd. Bekendheid en macht waren toen ook al een middel om ideeën te promoten. Zeker als de Europese elite zijn neus ophaalde voor wat uit Afrika kwam.

Later werd het pokkenvaccin door Edward Jenner geperfectioneerd, na zijn observatie van de melkmeisjes die koepokken kregen. En jawel, een zekere Thomas Jefferson beproefde het koepokkenvaccin ook op zijn 120 slaven, met succes, maar niet wreed ethisch.

En zie, een ziekte die in de twintigste eeuw nog 300 miljoen doden eiste, is nu uitgeroeid dank zij een ongeziene logistieke inspanning.

Aandachtige observatie van zieken kan dus artsen op een spoor zetten. Maar ook de observatie van gemeenschappen. Londen werd in de negentiende eeuw regelmatig gegeseld door de cholera. Met een erg hoge sterftekans. Een verbeterd rioleringssysteem bracht beterschap, maar men kon de vinger niet leggen op de haarden waaruit alles weer begon.

Tot dokter William Farr, geen clinicus maar een cijferfanaat-statisticus die nauwkeurig overlijdens bijhield met leeftijd, oorzaak en woonplaats zich boog over de overlijdens aan cholera. Dankzij datum en precieze woonplaats kon hij zelfs het huis traceren van waaruit die bepaalde epidemische golf was ontstaan. Alles manueel op stadsplannen overbrengen was werkelijk een titanenwerk. Zonder de hulp van computers uiteraard…

Zo werd de epidemiologie geboren. Die is niet meer weg te denken uit een modern gezondheidsbeleid. Je kan niet meer spreken over een epidemie zonder de curve van Farr erbij te halen. Die werd nog elke dag getoond tijdens de covidepidemie. En doet onderzoek van rioolwater naar covid ook niet denken aan de lokalisatie methode van Farr? Die de overheid zelfs een waarschuwingssignaal geeft vóór dat er mensen met symptomen opduiken.

Het romantische verhaal van de schimmel die door een open raam kwam binnenwaaien op een petrischaal stafylokokken van Alexander Fleming is wereldbekend.

Minder bekend is dat deze toevallige ontdekking van 1928 maar sinds Wereldoorlog II tot klinische toepassingen heeft geleid. Bij de ontdekking was de farmaceutische industrie amper geïnteresseerd. Industriële productie was ook niet voor de hand liggend.

De urgentie kwam er door de wetenschap dat zowat een derde van de soldaten overleden aan infecties van oorlogswonden. Het was een signaal om met militaire discipline grootschalig op te treden. Toen pas kwam een belangrijke productie van penicilline op gang.

Een mijlpaal, want het terugdringen van infecties door antibiotica en vaccins is historisch de belangrijkste medische bijdrage geweest tot een toename van de levensverwachting.

Dr. Karel DE KOKER

bestuurder MCH

Medische artikels

Cardiovasculair

ANTIHYPERTENSIVA EN NEVENEFFECTEN: NIET TE VERWAARLOZEN

Antihypertensives are effective at reducing the risk of cardiovascular disease, but limited data exist quantifying their association with serious adverse events, particularly in older people with frailty. This study aimed to examine this association using nationally representative electronic health record data.

Methods and findings

This was a retrospective cohort study utilising linked data from 1,256 general practices across England held within the Clinical Practice Research Datalink between 1998 and 2018. Included patients were aged 40+ years, with a systolic blood pressure reading between 130 and 179 mm Hg, and not previously prescribed antihypertensive treatment. The main exposure was defined as a first prescription of antihypertensive treatment. The primary outcome was hospitalisation or death within 10 years from falls. Secondary outcomes were hypotension, syncope, fractures, acute kidney injury, electrolyte abnormalities, and primary care attendance with gout. The association between treatment and these serious adverse events was examined by Cox regression adjusted for propensity score. This propensity score was generated from a multivariable logistic regression model with patient characteristics, medical history and medication prescriptions as covariates, and new antihypertensive treatment as the outcome. Subgroup analyses were undertaken by age and frailty. Of 3,834,056 patients followed for a median of 7.1 years, 484,187 (12.6%) were prescribed new antihypertensive treatment in the 12 months before the index date (baseline).

Antihypertensives were associated with an increased risk of hospitalisation or death from falls (adjusted hazard ratio [aHR] 1.23, 95% confidence interval (CI) 1.21 to 1.26), hypotension (aHR 1.32, 95% CI 1.29 to 1.35), syncope (aHR 1.20, 95% CI 1.17 to 1.22), acute kidney injury (aHR 1.44, 95% CI 1.41 to 1.47), electrolyte abnormalities (aHR 1.45, 95% CI 1.43 to 1.48), and primary care attendance with gout (aHR 1.35, 95% CI 1.32 to 1.37). The absolute risk of serious adverse events with treatment was very low, with 6 fall events per 10,000 patients treated per year. In older patients (80 to 89 years) and those with severe frailty, this absolute risk was increased, with 61 and 84 fall events per 10,000 patients treated per year (respectively). Findings were consistent in sensitivity analyses using different approaches to address confounding and taking into account the competing risk of death. A strength of this analysis is that it provides evidence regarding the association between antihypertensive treatment and serious adverse events, in a population of patients more representative than those enrolled in previous randomised controlled trials. Although treatment effect estimates fell within the 95% CIs of those from such trials, these analyses were observational in nature and so bias from unmeasured confounding cannot be ruled out.

Conclusions

Antihypertensive treatment was associated with serious adverse events. Overall, the absolute risk of this harm was low, with the exception of older patients and those with moderate to severe frailty, where the risks were similar to the likelihood of benefit from treatment. In these populations, physicians may want to consider alternative approaches to management of blood pressure and refrain from prescribing new treatment.

Author summary

Why was this study done?

The benefits of blood pressure–lowering treatment have been widely studied, with recent reviews of the scientific literature suggesting increasing benefit as patients get older.

The harms of blood pressure–lowering treatment are less well known, although another recent review of clinical trials showed that treatment is associated with acute kidney injury, hyperkalaemia (high blood potassium leading to medical complications), hypotension (low blood pressure) and syncope (fainting), but not falls or fracture.

However, the trials included in these reviews are likely to have limited external validity, since participants are typically highly selected and diligently supported by trial teams in a way that does not reflect routine clinical practice.

At present, there is little evidence to describe how the harms of antihypertensive treatment change as patients get older and develop frailty.

What did the researchers do and find?

This observational study utilised anonymised data from the electronic health records of patients in England. Those included were aged 40+ years, with high blood pressure, but had not previously been prescribed blood pressure–lowering treatment.

A statistical analysis was undertaken to examine whether patients prescribed a blood pressure–lowering medication were more likely to experience a serious adverse event sooner, compared to those who were not prescribed such medications.

In a total of 3,834,056 patients, blood pressure–lowering treatment was associated with an increased risk of hospitalisation or death from falls, hypotension, syncope (but not fracture), acute kidney injury, electrolyte abnormalities, and primary care consultations for gout.

These risks were much higher in older patients and those with frailty. For example, in those aged 40 to 49 years, 3,501 patients would need to be treated for 5 years to cause a serious fall. However, for those aged 80 to 89 years, only 33 patients would need to be treated for the same period to cause a serious fall.

What do these findings mean?

Blood pressure–lowering treatment was found to be associated with an increased risk of serious adverse events.

Across the whole population, the likelihood of experiencing this harm was very low.

However, in older patients (aged 80+ years) and those with moderate to severe frailty, the risk of harm was notably increased.

This analysis suggests that new prescription of blood pressure–lowering treatment in these older patients with frailty was just as likely to cause a serious fall, as it would prevent a stroke or heart attack.

https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1004223

Met dank aan dr. Lesly Vander Ginst

OORZAKEN EN AANPAK VAN POSTSCABIESJEUK

Het aantal scabiesbesmettingen is de afgelopen jaren fel gestegen, waardoor patiënten met hevige jeuk bij de huisarts of de dermatoloog terecht komen.

Etiologie en pathogenese:

- De besmetting gebeurt door Sarcoptes scabii var. hominis:
  - De vrouwelijke mijt graaft na bevruchting door een mannelijke mijt een ondiep gangetje door de hoornlaag van de huid.
  - Na de bevruchting overlijdt het mannetje en het vrouwtje legt eitjes, elke dag een paar, terwijl ze verder door de huid graaft.
  - De mijten leven van vocht en lymfe, maar ze nemen geen bloedmaaltijd.
  - Om de gangetjes te graven gebruiken ze hun speeksel.
- De mijten, de eitjes en de nymfen die daaruit voortkomen, en hun uitwerpselen veroorzaken samen een allergische reactie die in intense jeuk en huiduitslag resulteert.

Transmissie:

- Overdracht van de mijt kan van persoon tot persoon gebeuren:
  - Kan door direct huid-op-huidcontact gedurende minstens 15 minuten, zoals bij seksueel contact.
  - Kan ook door beddengoed of kleding te delen.
- Vaak komt scabies voor in situaties waarin mensen dicht op elkaar leven, zoals in studentenhuizen, kinderopvangcentra en verpleeghuizen.

Symptomatologie:

- Jeukklachten ’s nachts, hoofdzakelijk blaasjes en rode bultjes tussen de vingers, op de polsen,voeten en in de genitale regio: krabeffecten die hevig en langdurig aanwezig kunnen zijn.
- Daarnaast hebben psychosociale problemen, zoals angst voor herinfectie en schaamte met sociale isolatie als gevolg, een grote impact op de kwaliteit van leven.

Epidemiologie:

- Komt wereldwijd bij alle sociale klassen voor:
  - Uit gegevens van het Nederlands Centrum voor Beroepsziekten blijkt dat het jaarlijks aantal scabiesmeldingen in Nederland in de periode 2011-2021 gestegen is.
  - Vermoedelijk ligt het daadwerkelijk aantal besmettingen een stuk hoger.
- Er wordt in het laatste decennium een meer dan verdriedubbeling van het aantal scabiesbesmettingen gezien, en dan voornamelijk bij adolescenten en (jong)volwassenen.
- In diezelfde periode is het gebruik van scabicide medicatie zelfs vervijfvoudigd.

Diagnosestelling:

- Geschiedt op basis van de anamnese, het klinisch beeld, het lichamelijk onderzoek en aanvullende diagnostiek.
- Felle jeuk is het belangrijkste symptoom, vooral ’s nachts en vaak zonder voorgeschiedenis van huidziekten:
  - Veelvoorkomend is contact met mensen die ook jeuk hebben.
  - Kenmerkende huidafwijkingen: vesikels, papels, noduli en krabeffecten, meestal op de vingers, polsen, oksels, liezen, genitaliën en mammae.
- Dermatoscopie: hiermee kunnen de kenmerkende gangetjes en het ‘delta-wing-sign’ vastgesteld worden:

    - Men ziet aan het einde van de gang een donkere driehoek: het voorste deel van de mijt met de kop, de mond en de voorste poten.
    - Men noemt dit beeld het delta-teken, naar de Griekse letter delta..
- Mijten, eieren of scybala (fecespakketjes) worden aangetoond in een direct (KOH-)preparaat.
- Bestaat er twijfel over de aanwezigheid van scabies, en zijn de mogelijkheden voor microscopisch onderzoek of dermatoscopie beperkt, dan kan PCR-diagnostiek naar scabies uitkomst bieden.

Behandeling:

- Er zijn in Nederland drie middelen beschikbaar voor de behandeling van schurft: permetrine-5%-crème (Loxazol), ivermectinetabletten en benzylbenzoaatsmeersel 25% FNA.
- Adequate hygiënemaatregelen zijn naast deze behandeling essentieel:
    - Naleving van deze hygiënemaatregelen is een ware uitdaging.
    - Immers, onvolledige uitvoering hiervan geeft een risico op herbesmetting.
    - Eveneens cruciaal is het gelijktijdig behandelen van huisgenoten en (bed)partners.
- Scabicide middelen doden de mijten, en dat is de enige effectieve methode om jeuk blijvend te verminderen.
- Daarnaast kunnen antihistaminica, mentholpoeder en emolliens verlichting geven tijdens de behandeling.
- De jeuk neemt vaak toe direct nadat de behandeling begonnen is:
    - Komt omdat de mijten uiteenvallen, waardoor de type-IV-overgevoeligheidsreactie toeneemt.
    - Vaak stelt men ten onrechte de diagnose ‘recidief’ op basis van jeuk die nog enige tijd na de behandeling aanhoudt.
    - Deze jeuk kan tot zes weken na de behandeling aanhouden.
- Aantal behandelingen:
    - Iedereen met klachten: 2 behandelingen.
    - Huisgenoten en seksuele contacten zonder klachten: 2 behandelingen
    - Contacten zonder klachten: 1 of 2 behandelingen.
- Uitvoering:
    - Was alles op 60° of stop het 3 dagen in een vuilniszak.
    - Stofzuig alles van stof dat niet in de wasmachine of in vuilniszakken kan, zoals de bank, tapijt enz.
    - Huisdieren: raak ze de eerste 3 dagen van de behandeling zo min mogelijk aan.
- Was- en luchtmaatregelen:
    - Permetrinecrème: smeer het ganse lichaam in van de kaaksrand naar beneden tot en met onder de voeten; ook oksels, bilnaad, uitwendige geslachtsorganen en tussen de tenen.
    - Nagels kort knippen.
    - Smeer de crème met een oude tandenborstel onder de nagels.
    - Ivermectinetabletten: doseren op geleide van gewicht.
- Kinderen:
    - Smeer baby’s en kinderen < 12 jaar helemaal in, inclusief gelaat, behaarde hoofdhuid en de oren.
    - Smeer bij het verschonen van de luier opnieuw crème op de plekken waar de luier zit.
    - Denk eraan om bij kinderen ook de knuffels mee te nemen: was ze op 60° of doe ze 3 dagen in afgesloten vuilzakken.

Valkuilen was- en luchtmaatregelen uit de praktijk:

Valkuil	Onderbouwing
Kleding reinigen met stoomreiniger	Kleding dient gedurende > 10 minuten op 60° verwarmd te worden, zoals in een wasmachine; een stoomreiniger verwarmt kleding tijdens < 10 min.
Kleding buiten zetten gedurende 3 dagen	Scabiesmijt gaat vaak dood na 72 uur (3 dagen) buiten het lichaam bij 18-20°C; bij een lage buitentemperatuur daalt het metabolisme van de mijt en kan die tot 7 dagen overleven.
(Bed)partners niet gelijktijdig behandeld.	Hierdoor ontstaat een pingpongeffect.
Een item van stof toch vergeten mee te wassen of te luchten.	Herbesmetting van dit item.
Stoffen sneakers niet gedurende 3 dagen luchten.	Herbesmetting kan optreden door huidcontact met de stoffen schoen.

Resistentie:

- Ter zake is er veel onderzoek gedaan, maar deze studies zijn heterogeen en het is niet altijd duidelijk of vertekenende factoren ('confounders') beperkt of uitgesloten waren:
  - Er zijn in schurfmijten wel mutaties aangetroffen die mogelijk tot verminderde gevoeligheid voor ivermectine en permetrine leiden.
  - Tot op heden blijft het echter onduidelijk in welke mate er van resistentie sprake is.
- In de praktijk blijkt dat bij een persisterende infectie de behandeling toch vaak ineffectief geweest is als gevolg van een onjuiste uitvoering van de hygiënemaatregelen of de behandeling zelf.
- Herbesmetting is een andere oorzaak van persisterende scabies, omdat er weinig personen in de directe omgeving mee behandeld zijn.

Scabies en jeuk:

- De felle jeuk is kenmerkend voor scabies en deze kan zeer invaliderend zijn:
  - Deze ontstaat primair door de immunologische reactie op de mijt en diens bijproducten: t.t.z. speeksel en feces.
  - Er ontstaat hierdoor in de huid een directe en indirecte immuunrespons door cytokines.
  - Klinisch uit de vertraagde, cellulaire immuniteit zich in een beeld van eczeem met rode papels, erytheem en vesikels.
- Er ontstaan door de intense (nachtelijke) jeuk en het krabben secundaire huidafwijkingen in de vorm van

krabeffecten en geëxcorieerde papels en de huid kan ook secundair geïnfecteerd raken.

Postscabiesjeuk:

- De patiënt kan na een succesvolle behandeling last houden van jeuk en een aanhoudende immuunrespons speelt hierbij een belangrijke rol:
  - Betreft het aangeboren immuunsysteem en het complementsysteem.
  - De jeuk kan als gevolg hiervan weken tot maanden aanhouden.
- Staat bekend als postscabiesjeuk of – wanneer er huidafwijkingen aanwezig zijn – als 'persistent insect bite'.
- Het is erg belangrijk om het beeld te onderscheiden van actieve scabies of herbesmetting, een andere huidziekte of een huidreactie op de scabicide crème.
- Een atopische constitutie (eczeem, astma, hooikoorts, allergische rinitis) zijn risicofactoren voor postscabiesjeuk, naast oudere leeftijd.
- De jeukklachten kunnen door krabben in stand gehouden worden:
  - Het is van belang dat de patiënt hiervan op de hoogte gesteld wordt.
  - Adequate voorlichting kan samen met lokale behandelingen met hydraterende crèmes, mentholcrème of een lichte corticosteroïdcrème de jeukklachten helpen verminderen.
  - Men kan ook een sederend of niet-sederend antihistaminicum voorschrijven.

Scabiesgeïnduceerde infestatiewaan:

- Een eerdere scabiasbesmetting kan soms een infestatiewaan veroorzaken:
  - Betreft een zeldzame psychiatrische aandoening.
  - Het is volgens de DSM-5 een waanstoornis van het somatische type, met zowel een primaire als een secundaire variant.
- De secundaire variant kan het gevolg zijn van andere psychiatrische aandoeningen, medicatiegebruik of middelengebruik: zo kan gebruik van amfetamine en cocaïne een infestatiewaan uitlokken.
- Vaak presenteren deze patiënten zich bij de dermatoloog met jeukende huidafwijkingen:
  - Meest beschreven vermeende veroorzakers zijn insecten, wormen of vezels.
  - Men ziet vaker dat patiënten scabies als oorzaak aanwijzen omdat het aantal besmettingen met scabies is toegenomen.
- Vaak brengen patiënten één of meerdere monsters mee van de huid of de vermeende veroorzakers, het zogenoemde 'specimen sign'.
- Dermatologische aandoeningen moeten om de diagnose te kunnen stellen uitgesloten worden op basis van lichamelijk onderzoek en eventueel aanvullend microscopisch onderzoek.
- Differentiaaldiagnose van een infestatiewaan:
  - Hier staan ook somatische aandoeningen, intoxicaties en psychiatrische stoornissen.
  - Aanbeveling geldt om deze alternatieve oorzaken uit te sluiten met screenend bloedonderzoek en urinescreening op cocaïne en amfetamine.
  - Het is wenselijk om samen te werken met een psychiater.
- De behandeling van een infestatiewaan:
  - Deze is uitdagend vermits de patiënt en de zorgverlener over de oorzaak van de klachten van mening verschillen.
  - Hoeksteen van de behandeling wordt gevormd door antipsychotica.
- Om de patiënt te motiveren voor medicamenteuze behandeling of psychotherapie is het essentieel om een therapeutische relatie op te bouwen waarin de patiënt zich serieus genomen voelt.

Besluit:

- Jeuk na scabies vormt een uitdagend probleem en heeft een grote impact op het mentale welzijn.
- Men moet ervoor waken om dit niet al te gemakkelijk te wijten aan een herbesmetting:
  - Als er geen aanwijzingen zijn voor scabies, dan moeten er andere

mogelijke oorzaken in overweging genomen worden.
- Bij herbesmetting is het van belang om de tijd te nemen om eventuele onzorgvuldigheden in de uitvoering van de therapie , hygiënische maatregelen en wasprocedures op te sporen.

Ned Tijdschr Geneeskd 14 december 2023 pag. 10-16.

Met dank aan dr. Willy Storms

KAN VERHOOGD SCHILDKLIERHORMOON EEN COGNITIEVE STOORNIS UITLOKKEN ?

Naar aanleiding van recent onderzoek (JAMA Intern Med 2023; online 1 oktober) bevelen Amerikaanse auteurs aan dar zorgverleners extra waakzaam moeten zijn voor overdosering van schildklierhormoon bij oudere patiënten.

Enkele cijfers:

- Daartoe onderzochten ze gegevens van de elektronische patiëntendossiers van 65.931 patiënten in de eerstelijnszorg in de periode 2014-medio 2023.
- Ze zochten hierin naar 65-plussers die voorafgaand aan hun eerste huisartsenbezoek in de onderzoeksperiode nog geen thyreotoxicose doormaakten (gedefinieerd als een TSH-waarde < 0.45 mIU/L) en ook geen cognitieve diagnose.

Uitvoering:

- Vervolgens gebruikten de onderzoekers een tijdvariabel Cox-model om na te gaan of er een verband was tussen het optreden van thyreotoxicose en een latere cognitieve stoornis.
- Deze werd geïdentificeerd aan de hand van gerelateerde ICD-10-codes (ICD = International Classification of Diseases).
- Er waren iets meer vrouwen die meededen (56%) en bij 4,1% van de deelnemers werd een verlaagde TSH-waarde gemeten:
  - Dit kwam meestal door een te hoge dosis schildklierhormoon (iatrogeen: 60%).
  - De TSH-waarden waren wel beduidend lager bij een endogene thyreotoxicose door hyperthyreoïdie.
  - Bedroeg < 0,1 mIU/l bij 42% van de metingen versus 31% bij iatrogene thyreotoxicose.

Resultaat:

- Thyreotoxicose hing samen met een verhoogd risico op een cognitieve stoornis (aangepaste hazardratio (aHR) : 1,39; 95%-BI: 1,18-1,64).
- Bij een onderverdeling naar de oorzaken bleek dat alleen thyreotoxicose door een iatrogene overdosering samenhing met een verhoogd risico op een cognitieve stoornis (aHR: 1,34; 95%-BI: 1,10-1,63).
- Er bleek ook dat het risico op een cognitieve stoornis groter was naarmate de overdosering ernstiger was (aHR: 1,65; 95%-BI: 1,20-2,28).
- Een verband tussen de diagnose ‘hypothyreoïdie’ en een cognitieve stoornis als mogelijke confounder werd er door de onderzoekers niet gevonden.

Beschouwing:

- Bij de onderzoekers heerst het vermoeden dat de samenhang die zij gevonden hebben op een causaal verband wijst omwille van de hogere kans op een cognitieve stoornis naarmate er een ernstiger overdosering was van schildklierhormoon:
  - Wel wijzen ze erop dat dit dossieronderzoek voor coderingsfouten gevoelig is.
  - Er ontbreekt o.a. informatie over de aard en de ernst van de cognitieve diagnoses.

- De auteurs waarschuwen voor een overdosering met schildklierhormoon bij oudere mensen met een hypothyreoïdie.

Besluit:

- Sinds enkele jaren wordt het voorschrijven van schildklierhormoon aan oudere mensen met subklinische hypothyreoïdie actief ontraden.
- De auteurs maken niet precies duidelijk in welke mate het vroegere voorschrijven van schildklierhormoon bij oudere mensen met subklinische hypothyreoïdie mogelijk nog heeft bijgedragen aan het verhoogde risico op een cognitieve stoornis in dit onderzoek.

Ned Tijdschr Geneeskd 7 december 2023 pag. 42.

Met dank aan dr. Willy Storms

HET OUDER WORDEN MEDICALISEREN: TOCH PROBEREN OM DIT TE (VER)MIJDEN

Jos Schols is hoogleraar ouderengeneeskunde aan de Universiteit Maastricht en ziet een aantal kantelpunten in de geschiedenis van de ouderenzorg en ouderengeneeskunde – beoordeling van situatie in Nederland.

Inleiding van zijn zienswijze:

- Verpleeghuizen zijn begonnen als gestichten, een soort 'opberghuizen':
  - Deze boden onderdak aan mensen voor wie in het ziekenhuis geen plaats meer was.
  - Er was ook plaats voor andere doelgroepen waar in de samenleving moeilijk plek voor te vinden was .
- Er was een eerste kantelpunt in 1968, toen de Algemene Wet Bijzondere Ziektekosten (AWBZ) ingevoerd werd:
  - Verpleeghuizen kropen uit hun schulp, waarbij de zorg steeds meer verleend werd vanuit een concept.
  - Dit laatste kon omschreven worden als continu, langdurig, systematisch en multidisciplinair.
  - Er kwamen naast verpleegkundigen en verzorgenden andere beroepsgroepen werken zoals fysiotherapeuten en ergotherapeuten.
- Later kwamen er ook psychotherapeuten en geestelijke verzorgers + natuurlijk eigen dokters:
  - Ze werden destijds verpleeghuisartsen genoemd, nu specialisten ouderengeneeskunde.
  - Daarmee zijn wij (= Nederland) het enige land waar al deze professionals ook in dienst zijn van het verpleeghuis.

D*e verdere ontwikkeling van het vak verpleeghuisgeneeskunde sinds de invoering van de AWBZ*;

- Het vakgebied werd in 1990 erkend en inmiddels was er een beroepsvereniging , namelijk de Nederlandse Verenging van Verpleeghuisartsen, nu bekend als Verenso:
  - Om het vak echt te professionaliseren was dit nodig.
  - Het was overigens in die tijd al duidelijk dat men deze kennis ook in de eerste lijn kon doorzetten.
- Het heeft echter lang geduurd alvorens men in de eerste lijn zichtbaar werd. en eigenlijk is er nog steeds geen sprake van de 'community geriatrician', zoals in feite beoogd werd.

Wat moet er dan veranderen om de ouderenzorg houdbaar te houden ?

- Er zal in de eerste lijn op de eerste plaats veel meer aandacht moeten komen voor preventie:
  - Men moet mensen leren om gezond oud te worden, en hierdoor ook een stuk verantwoordelijkheid bij de burgers zelf leggen.
  - Over levensloopbestendige huisvesting en over de vraag hoe ze om zich heen ondersteuning kunnen vinden, zullen mensen tijdig en proactief moeten nadenken.
- Ze moeten verder tijdig leren hoe ze hun weg kunnen vinden in het doolhof van voorzieningen:
  - Momenteel zijn er nog te veel mensen die denken: ik heb premie betaald, straks moeten jullie maar voor mij zorgen.
  - Men moet als zorgverlener niet te snel geneigd zijn om zaken over te nemen.

Bij wie ligt dan de taak om ouderen gezond ouder te laten worden ?

- Denkelijk ligt de primaire rol bij de publieke gezondheidszorg, denk bvb. aan de GGD's,

maar ook huisartsen kunnen hier een stimulerende rol spelen.

- In de toekomst moet er misschien wel een ‘consultatiebureau’ voor ouderen komen, al moet men het ouder worden niet te snel medicaliseren:
  - Ouderen moet men hoe dan ook blijven uitdagen om aan bewegingsactiviteiten mee te doen en gezond te eten.
  - Geldt trouwens niet alleen voor ouderen, maar ook voor jongeren.
- Betreft programma’s die tijdens de ganse levensloop ingezet zouden moeten worden:
  - Rust roest, ook sociaal, immers sociale participatie draagt bij aan betekenisvol ouder worden.
  - Overigens zijn dit geen primaire taken voor een specialist ouderengeneeskunde en geriater.

Ned Tijdscht Geneeskd 21 december 2023 pag. 51.

Met dank aan dr. Willy Storms

DIGITALE KOERS OF TOCH BEST NIET

Jan Festen is 85 jaar oud, is gepensioneerd longarts, zet zich in als patiëntvertegen-woordiger voor ouderen en ziet twee kantelpunten in de zorgtoediening, namelijk samen beslissen en digitalisering van de zorg.

Wat verstaat hij onder 'samen beslissen' ?

- Voorheen legde de arts de behandeling aan de patiënt voor:
  - Deze kon eigenlijk altijd alleen maar 'ja' zeggen.
  - Nu heeft er een verschuiving plaatsgevonden naar samen beslissen.
- Belangrijkste hierbij is dat artsen hun patiënten in hun hele context zien:
  - Wie hebben ze voor zich zitten en wat is hun levensperspectief ?
  - Waar komt het eventuele besluit dat ze zullen nemen vandaan ?
- Alle behandelopties moet de arts aan de patiënt voorleggen en hij moet uitleggen wat de gevolgen ervan zijn, ook wat betreft de kwaliteit van leven:
  - Op die manier kan er een weloverwogen besluit genomen worden.
  - Kan ook inhouden dat er geen medische behandeling meer plaatsvindt.
- Dat zal in het begin meer tijd vergen, maar finaal levert dit winst op.

Geldt dit laatste ook voor 'digitalisering van de zorg '?

- Je kan stellen, in zekere zin wel, immers onder patiënten leeft er een grote variatie aan digivaardigheid.
- Maakt dat artsen aan hun patiënten uitdrukkelijk een aantal vragen moeten stellen:
  - Is die digitale wereld iets voor jou: kan je dat en/of wil je dat ?
  - Ga er maar niet van uit dat dit voor iedereen weggelegd is !

Voordelen voor digitalisering:

- Vooral de monitoring en ondersteuning is voor veel patiënten een grote toevoeging:
  - Ze kunnen bvb. thuis een ecg maken of de BD meten.
  - De arts kan dat dan gelijktijdig uitlezen.
- Ze worden eraan herinnerd dat ze hun medicatie moeten innemen en ze kunnen uitslagen en verslagen on line inzien.

Nadelen van digitalisering:

- Belangrijk nadeel: er vindt minder vis à vis contact plaats en dat maakt de zorg niet per se prettiger.
- Je moet daarnaast de resultaten wel kunnen interpreteren:
  - Überhaupt moet je vaardig genoeg zijn om bij je gegevens te kunnen.
  - En dat is lang niet iedereen !
- Men moet wellicht ook uitkijken met aannames:
  - Het cohort dat nu wel gebruik kan maken van de digitale foefjes kan dat misschien straks niet meer.
  - Komt omdat de ontwikkelingen haast te snel gaan om bij te benen.

De gouden tip voor huisartsen:

- Ze moeten leren de taal van de patiënten te verstaan en hierbij aan te sluiten, m.a.w. wat bedoelt een patiënt echt ?
  - Uit onderzoek en ervaringen blijkt dat de arts de patiënt vaak snel onderbreekt.
  - Dit terwijl patiënten vaak tijd nodig hebben om hun verhaal aan het licht te

brengen, en andere denkkaders hebben dan de arts.

- De afgelopen jaren zijn er grote stappen gemaakt qua communicatie, maar daarin valt ook nog veel te winnen om samen tot een goed besluit te komen.

Korte overweging: kantelpunten zijn momenteel overal, dus ook op geneeskundig vlak, we zitten met een verouderd concept, dat niet meer past in het tijdsgewricht, en dus komt het er op aan om een nieuw evenwicht te vinden, voor ons vooral tussen (huis)arts en patiënt: een belangrijke opdracht en ingreep !

Ned Tijdscht Geneeskd 21 december 2023 pag. 55.

Met dank aan dr. Willy Storms

Gynaecologie

EUG: RISICOFACTOREN, VASTSTELLING EN AANPAK

Zeven op de 1000 geboorten in Nederland betreft een extra-uteriene graviditeit (EUG) en deze is niet altijd gemakkelijk te herkennen.

Risicofactoren:

- Ze verhogen de kans op een EUG, en dus is alertheid geboden:
  - Zo kunnen alle factoren die het transport van het embryo naar de uterus vertragen het risico verhogen, zoals tubapathologie.
  - Komen ook in aanmerking: eerdere EUG, PID (Pelvic Inflammatory Desease) in de voorgeschiedenis, subfertiliteit, congenitale afwijkingen tubae en tubachirurgie.
- De kans op een EUG is ook groter na een fertiliteitsbehandeling en bij vrouwen die zwanger zijn terwijl ze een (hormoon)spiraal hebben of na sterilisatie.
- Er wordt echter bij 50% van de EUG's geen aanwijsbare oorzaak gevonden.
- Een EUG kan snel problemen geven en levensbedreigend zijn:
  - Er zijn echter ook EUG's die, afhankelijk van locatie en groeisnelheid, minder acuut levensbedreigend zijn.
  - Er is dan dus meer tijd alvorens er mogelijk levensbedreigende complicaties ontstaan.
- Het grootste gevaar van een EUG schuilt in een tubaruptuur, waarbij de patiënt snel veel bloed intra-abdominaal kan verliezen.

Klachtenpatroon:

- EUG geeft meestal klachten voor de achtste zwangerschapsweek:
  - 95% van de EUG's, het overgrote deel dus, is gelokaliseerd in de tuba.
  - Pijnklachten ontstaan hier bij groei van het embryo.
- Bij nieuw ontstane (hevige) buikpijn, eventueel in combinatie met vaginaal bloedverlies in de fertiele levensfase en tijdens de vroege zwangerschap, moet men alert zijn.
- Bij 65% van de EUG's komt de klassieke combinatie van buikpijn en vaginaal bloedverlies voor:
  - De patiënt vertoont pijn bij palpatie van de onderbuik en soms zijn er tekens van peritoneale prikkeling.
  - Kan gaan om druk- of loslaatpijn van de onderbuik en défense musculaire, met positieve likelihood ratio's van respectievelijk 3,7 en 8,0.
- Er kan bij een vaginaal toucher sprake zijn van slingerpijn en een gevoelig cavum Douglasi.:
  - Een vaginaal toucher heeft overigens een beperkte toegevoegde waarde.
  - Speculumonderzoek heeft geen toegevoegde waarde.
- Klachten die passen bij een levensbedreigende tubaruptuur:
  - Deze wijzen op ruim bloedverlies/een bedreigde circulatie, o.a. een hoge pols, lage BD en neiging tot collaberen.
  - Felle buikpijn/peritoneale prikkeling, schouderpijn (als teken van 'referred pain') en loze aandrang voor defecatie kunnen daarnaast ook aanwezig zijn.

- Wanneer er sprake is van klinische instabiliteit stuurt men zo'n dame direct met spoed door naar de gynaecoloog.

Zwangerschapstest:
- Bij vermoeden van een EUG moet de patiënt een zwangerschapstest doen:
  - Moet gebeuren wanneer die nog niet verricht is.
  - Moet ook gebeuren bij twijfel over de betrouwbaarheid van de afname/anamnese.
- Een negatieve zwangerschapstest sluit een EUG echter niet uit:
  - De zwangerschapstest kan in een zeer vroeg stadium nog negatief zijn.
  - Het is echter zeer onwaarschijnlijk dat het bloedverlies of de buikpijn dan al door een EUG

  veroorzaakt wordt.
- Men kan nagaan of er al een echo verricht is wanneer al bekend was dat de patiënt zwanger is, en zo'n echo is mogelijk vanaf 6 weken zwangerschapsduur.
- Een bewezen intra-uteriene zwangerschap sluit een EUG zo goed als uit:
  - Een tweede zwangerschap in de tuba naast een intra-uteriene zwangerschap is zeldzaam.
  - Gaat namelijk om 1 op^15.000 zwangerschappen.
- Men kan bij buikpijn en een positieve zwangerschapstest naast een EUD differentieeldiagnostisch denken aan een spontaan miskraam, bloedverlies bij een intacte intra-uteriene zwangerschap, PID, torsie van een ovarium, een corpusluteumbloeding, appendicitis en nierstenen.

Verwijzing en behandeling:
- Bij vermoeden van een EUG moet men de patiënt direct naar de gynaecoloog verwijzen voor een diagnosestelling via een echo en serum-HCG-bepaling:
  - Immers snelle diagnostiek verhoogt de kans op een tubasparend beloop.
  - De keuze voor de behandeling hangt af van de termijn, de lokalisatie en de klachten, wanneer de zwangerschap inderdaad buitenbaarmoederlijk is.
- Kan ook zijn dat de diagnose niet direct duidelijk is, en dan spreekt men van een zwangerschap op onbekende locatie (ZOL):
  - De ZOL wordt vervolgd zolang als de patiënt hemodynamisch stabiel is.
  - De locatie van de EUG wordt in de loop van de tijd soms wel duidelijk.
- De opties voor de behandeling van een EUG zijn de volgende:
  1. Chirurgisch ingrijpen met tubectomie of tubotomie (bij deze laatste ingreep wordt de tuba gespaard).
  2. Medicamenteuze behandeling met metotrexaat – dit is een cytostaticum dat DNA-synthese en de vorming van nieuwe cellen remt.
  3. Een afwachtend beleid met vervolgen van HCG-bepaling – hierbij kan alsnog gekozen worden voor behandeling wanneer het HCG blijft stijgen.
- De keuze tussen de verschillende behandelingen voor de patiënt hangt samen met zijn stabiliteit, de HCG-waarde en de lokalisatie van de EUG.

Een volgende zwangerschap:
- Door schade aan of verlies van de tuba is de fertiliteit na een EUG afgenomen.
- Door mobiliteit van de contralaterale tuba wordt deze voor een deel gecompenseerd.
  - Deze kan immers ook bevruchtingen van de contralaterale zijde oppakken.
  - Een volgende zwangerschap heeft een risico van 2-25% op een herhaling van een EUG –

  men moet daar dus alert op zijn.

Besluit:

- Tijdens een prille zwangerschap moet men buikpijn, met of zonder vaginaal bloedverlies, met urgentie beoordelen.
- Wanneer vrouwen in de fertiele levensfase (hevige) buikpijn hebben, moet men een EUG als oorzaak overwegen:
  - Bij risicofactoren voor tubapathologie is de kans op een EUG groter.
  - Toch is het zo dat de helft van de EUG's voorkomt zonder dat er een duidelijke oorzaak gevonden wordt.
- Intra-abdominaal bloedverlies bij een EUG kan leiden tot een levensbedreigende situatie, waarbij snel handelen geboden is.
- Soms zijn er via de gynaecoloog meerdere behandelingen mogelijk, wanneer de patiënt hemodynamisch stabiel is.

Huisarts & Wetenschap december 2023 pag. 44-45.

Met dank aan dr. Willy Storms

Nachtelijk zweten

NIGHT SWEATS: WHAT YOU NEED TO KNOW

Night sweats are commonly reported, with a broad differential including both benign and life threatening causes

A detailed history, including characterising and contextualising the night sweats, and physical examination will help guide probability of certain conditions and help focus testing

Patients presenting with night sweats who have high risk signs or symptoms and host factors warrant further work-up, including complete blood count, inflammatory markers, and other testing guided by history and physical exam

For patients without concerning or high risk features, re-assessment 2-4 weeks after initial presentation before pursuing laboratory evaluation may be appropriate

Night sweats have historically been poorly defined, but generally can be thought of as excessive sweating that occurs during night time.The reason clinicians often ask about “night sweats,” as opposed to “day sweats” is that the threshold to sweat is lower at night. Thus, a condition such as tuberculosis that causes intermittent temperature rise would be more likely to lead to sweating at 3 am as opposed to 3 pm.

Night sweats are commonly reported across various settings. In one systematic review, prevalence estimates ranged widely across difference countries, healthcare settings, and populations.Estimates were 4.4% in a random population sample in South East Asia, 10% among US patients over 65 years old presenting to primary care, and 16% in a UK cohort of patients admitted to hospice.Data underlining the epidemiology of night sweats remains hampered by lack of standard definition and frequent association with multiple concurrent symptoms, leading to few studies reporting on night sweats as an isolated symptom.

Although night sweats can be associated with a decrease in quality of life, not all causes are dangerous. Causes can be categorised into three major categories: inflammatory (such as infection or malignancy), endocrine (such as menopause or hyperthyroidism), and other (such as medications, environmental, neurologic causes, sleep disorders) as seen in box 1. Given the many potential causes of varying severity, it is vital for clinicians to know the initial evaluation as well as important prompts for further investigation and testing.

Box 1: Potential causes of night sweats

Inflammatory aetiologies

- Infection
- HIV (acute infection and sequela of AIDS)
- Tuberculosis
- Infective endocarditis
- Acute mononucleosisand acute respiratory viruses
- Geographic infections:
  - Vector-borne diseases (such as Lyme disease, babesiosis, anaplasmosis, malaria, dengue fever)
  - Endemic fungi (such as coccidiomycosis)
- Malignancy
  - Leukaemia
  - Lymphoma
  - Solid organ malignancies
- Autoimmune
- Sarcoidosis
- Rheumatoid arthritis
- Giant cell arteritis

Endocrine or metabolic aetiologies

- Hyperthyroidism
- Alteration in oestrogen (menopause) or androgen levels (hypogonadism)
- Phaeochromocytoma
- Hypoglycaemia

Other aetiologies

- Drugs
- Medications that could cause hypoglycaemia
- Selective serotonin reuptake inhibitors
- β blockers
- Cholinesterase inhibitors and anticholinergics
- Anti-pyretic (paracetamol (acetaminophen), aspirin)
- Sleeping environment
- Gastro-oesophageal reflux
- Obstructive sleep apnoea
- Substance use or withdrawal (including alcohol)

Characterising and contextualising night sweats

The initial differential of a patient presenting with night sweats will vary significantly by practice setting, geographic location, and associated symptoms. Box 2 highlights key elements of the history and physical exam in order to characterise and contextualise the patient's night sweats, in order to narrow the differential and guide initial investigations.

Characterising night sweats includes asking about the frequency, duration, and severity of the night sweats. For example, a clinician could ask whether the sweating is severe enough to prompt the patient changing their clothes or bedding in the middle of the night. Nightly drenching sweats for two weeks should prompt more concern than intermittent, mild sweats over the prior year.

Contextualising the patient's night sweats involves asking about associated symptoms with a thorough review of systems as well as epidemiologic risk factors for different pathologies. For example, if the patient had noted an associated unintentional weight loss of 11 kg and lymphadenopathy, this would raise suspicion for lymphoma. Box 2 highlights high risk signs, symptoms, and host factors that should raise suspicion for infection or malignancy.

What is the next investigation?

Box 2: Key elements of history and physical exam when evaluating patients who report night sweats

History of present illness and review of systems

- Characterise night sweats—Assess duration, frequency, and severity of night sweats
- Contextualise night sweats—Review of systems to assess for associated symptoms
- Known contact with an individual with a communicable infectious disease (such as respiratory viruses, tuberculosis)*

Past medical history

- Immunocompromised status (including HIV/AIDs, malignancies being treated with chemotherapy, solid organ or bone marrow transplant recipients, and immunosuppressing drugs)*
- Personal history of malignancy*
- History of untreated latent tuberculosis*
- Medications (Review medication list for medications associated with night sweats (see box 1))

Social history

- Country of birth

Remote and recent travel history

Sexual history including type of intercourse, number of partners, and use of barrier protection (high risk if multiple recent partners without consistent barrier protection)*

Occupational history

- Tobacco, alcohol, and other recreational drug use
- Active intravenous drug use*

Family history

- First degree family member with history of malignancy*

Physical exam

- Vital signs
- Fever or other vital sign abnormality*
- Unintentional weight loss*
- Complete physical exam
- Lymphadenopathy*
- New cardiac murmur*
- Rash*
- Evidence of easy bruising or spontaneous bleeding*

**Denotes high risk sign, symptom, or host factor*

There is no published literature evaluating diagnostic strategies for the work-up of night sweats. Proposed diagnostic algorithms are limited in their acceptance because of the lack of standardised definition of night sweat severity, inclusion of specialised procedures not readily available in primary care settings (such as bone marrow biopsy), and lack of current evidence that one approach is superior to the others. Patients with high risk signs, symptoms, or host factors (as listed in box 2) should prompt additional diagnostics to assess for systemic inflammation, similar to the work-up our patient underwent.

Additional testing should be targeted and based on history and physical examination. Further initial testing may include serum creatinine levels, liver function tests, and chest radiography. For example, for patients with an increased risk of development of lung cancer (such as tobacco smokers), tuberculosis risk factors (living in a high incidence area, history of latent tuberculosis, or known tuberculosis exposures), or who report respiratory symptoms, a chest radiograph would be an appropriate initial investigation. The sensitivity and specificity will depend on the disease process of concern, but, as an example, the absence of any abnormality on chest radiography can have high sensitivity (94%) for active pulmonary tuberculosis. For other

patients who report associated heat intolerance and palpations, hyperthyroidism should be considered and checking thyroid stimulating hormone (TSH) levels is recommended as an initial test.

Box 3: Making sense of C reactive protein assays

C reactive protein (CRP) is an acute phase reactant that is produced in response to cytokines, especially interleukin . The upper limit of normal at our hospital is 5 mg/L, but different assays have different normal ranges, and the CRP can be up to 10 mg/L in healthy individuals. CRP is a sensitive test for many inflammatory aetiologies that could cause night sweats such as active tuberculosis in patients living with HIV and infective endocarditis but may be less sensitive for other conditions such as osteomyelitis and some malignancies. CRP is more helpful in its extremes, and one should always consider the clinical context for which it was requested. A negative CRP in the setting of a low pre-test probability for infection or malignancy is relatively reassuring (though cannot rule out an inflammatory process), and a very high CRP, though non-specific, should prompt further investigation.

Table 1 lists multiple endocrine, infectious, and malignant aetiologies of night sweats and includes guidance on when diagnostics for those conditions should be pursued and diagnostic accuracy of selected tests. For patients presenting with less severe night sweats (such as intermittent night sweats that do not lead to change in clothes or bed linen), without other concerning or high risk features, a watchful waiting approach for two to four weeks followed by re-evaluation may be appropriate before pursuing laboratory evaluation.

Table 1: Selected aetiologies of night sweats and associated diagnostics

Condition	When to consider testing	What initial tests to order	Test characteristics
Endocrine abnormalities			
Hyperthyroidism	Associated symptoms of heat intolerance, palpitations, anxiety, weight loss, increased frequency of bowel movements	TSH	Sensitivity 86-95%, specificity 92-95%
		Free thyroxine (T4)	Sensitivity 82%, specificity 94%
Alteration in oestrogen or androgen levels (such as menopause, male hypogonadism)	Women: Consider age, menstrual history, surgical status, symptoms of night sweats, hot flashes, and vaginal dryness	Clinical diagnosis; routine measurement of FSH not recommended Exceptions: Obtaining FSH level is recommended for women with underlying menstrual irregularities (such as polycystic ovarian syndrome), history of hysterectomy, or endometrial ablation, and age <40 years	N/A
	Men: History of androgen deprivation therapies (surgical or chemical), decreased libido, decreased spontaneous erections, erectile dysfunction	Morning fasting testosterone level	Normative range for testosterone levels varies among assays. Low testosterone levels should be confirmed on at least two morning blood samples

Condition	When to consider testing	What initial tests to order	Test characteristics
Infectious disease			
Active pulmonary tuberculosis	Respiratory symptoms with appropriate risk factors (such as person living with HIV, known active tuberculosis contact, residence in a country with high incidence of disease, travel to endemic regions)	Chest radiography	Any abnormality: Sensitivity 94%, specificity 89% Abnormality suggestive of pulmonary tuberculosis: Sensitivity 85%, specificity 96%
		Sputum for *Mycobacterium tuberculosis* nucleic acid amplification test	Xpert: Sensitivity 85-88% (98% for AFB smear positive and 67% for AFB smear negative), specificity 96-98%
HIV/AIDS	Not tested for HIV in past or prior negative test but subsequent high risk of exposure (such as multiple sexual partners, injected drug use)	Symptoms >2 weeks: Current generation antibody/antigen testing	Fourth generation antibody/antigen (screening in patients in high prevalence population): Sensitivity 79.8%, specificity 99.9%
		Symptoms <2 weeks: Current generation antibody/antigen testing and HIV viral load	HIV quantitative viral load (symptoms consistent with primary HIV): Sensitivity 100%, specificity 97.4%
Endocarditis or occult bacteraemia	Presence of concurrent fevers, new cardiac murmur, embolic stigmata in extremities	Blood culture	One set: 73-80% sensitivity for bacteraemia, may be more sensitive in endocarditis

Condition	When to consider testing	What initial tests to order	Test characteristics
Haematology/oncology			
Acute leukaemia	Bleeding, spontaneous bruising	Peripheral blood smear	No published test characteristics of peripheral smear
Chronic myeloid leukaemia	Splenomegaly, early satiety	Complete blood count with differential	Absolute basophil count $\geq 0.43 \times 10^9$/L: Sensitivity 93.9%, specificity 95.2%
Lymphoma	Lymphadenopathy, weight loss	LDH	≥2 time above upper limit of normal: Sensitivity 56%, specificity 85%
		Cross-sectional imaging (CT torso or PET)	CT torso: Sensitivity 70%, specificity 100%23
			PET/CT: Sensitivity 99%, specificity 100%
Solid organ malignancy	Localising symptoms, weight loss, personal or first degree relative with history of malignancy	Cross-sectional imaging (CT torso)	Difficult to quantify test characteristics for solid malignancies in general
		Disease-specific tumour markers (PSA for prostate)	Sensitivity 93%, specificity 20%

TSH=thyroid-stimulating hormone. AFB=acid-fast bacilli. LDH=lactate dehydrogenase. CT=computed tomography. PET=positron emission tomography. PSA=prostate-specific antigen.

https://www.bmj.com/content/381/bmj-2022-073982

Met dank aan dr. Lesly Vander Ginst

BEHANDELING VAN NEUROPATHISCHE PIJN, BIJ DIABETES MAAR OOK IN ANDERE GEVALLEN: COMBINATIE IS NUTTIG

Diabetes can cause nerve damage that can lead to diabetic peripheral neuropathy. One in four people with diabetes has painful diabetic neuropathy, and for most the pain is persistent. It often leads to poor sleep and quality of life, as well as mood disorders such as depression.

Guidelines from the National Institute for Health and Care Excellence (NICE) recommend medications, including amitriptyline, duloxetine, and pregabalin, for pain relief. But these treatments taken alone provide only partial benefit; pain severity drops by about half in around half of people. The drugs may have side effects such as dry mouth, dizziness, and nausea.

Many clinicians prescribe two medications for people whose pain is not adequately controlled by one. However, little evidence supports using these drugs in combination. Researchers investigated the effectiveness and safety of drug combinations for painful diabetic neuropathy.

What did the study do?

The study included 130 people with painful diabetic neuropathy. They were being treated at 13 primary and secondary care centres in the UK.

People were randomly allocated to one of three treatment pathways:

- Amitriptyline with pregabalin, if needed
- Duloxetine with pregabalin, if needed
- Pregabalin with amitriptyline, if needed.

People took the first drug for six weeks; the second was added for a further 10 weeks if the pain was not controlled. They then moved on to another pathway. For each pathway, the dose of the drug was gradually increased to the level a person could tolerate (without the side effects becoming too much).

The study design intended for people to complete the pathways one after the other (in a randomised order) for approximately 50 weeks overall. Some people dropped out of the trial itself, but 84 completed at least two pathways.

The researchers found that, during the final week of each pathway:

All three treatment pathways reduced pain to a similar degree

Treatments in combination provided additional pain relief in some people whose pain did not respond to one medication alone.

Sleep and quality of life were improved to a similar degree for all three pathways; and the costs for each of the pathways were roughly the same.

Side effects were as expected for each drug. For instance, several people experienced dizziness with pregabalin, nausea with duloxetine, and dry mouth with amitriptyline. The three pathways had similar numbers of serious side effects. Combination treatment was generally well tolerated, and few people discontinued treatment. People were most likely to continue with pregabalin supplemented by amitriptyline.

Why is this important?

The study should reassure clinicians that any of these drugs, or drug combinations, can provide effective pain relief. Combination treatment was safe, and helped people whose pain was not

adequately managed with one medication. All the trialled combinations of pregabalin, amitriptyline, and duloxetine provided similar pain relief.

One of the study's strengths is that it reflects clinical practice, the researchers say. Most patients start taking one medication and need to begin taking another after a few months if their pain is still not managed.

The study took longer to carry out than other clinical trials, which may partly explain why one in three people did not complete the planned 50 weeks.

What's next?

Clinicians could discuss the benefits and drawbacks of each medication with patients, to explore their preferences. The best treatment pathway for an individual may depend on the side effects people experience.

The study was not set up to compare single versus combination therapy. However, the findings suggest that people whose pain is not managed adequately with one medication could be treated with two, the researchers say.

This study included people with painful diabetic neuropathy. But many others experience painful neuropathy from other causes (such as cancer or multiple sclerosis). Overall, almost one in 10 people in the UK has painful neuropathy. Treatments (including the medications from this study) and guidelines for painful neuropathy are similar, regardless of the cause. Therefore, the findings from this study may be applicable to neuropathic pain caused by other conditions. The researchers say NICE could consider updating its guidelines on the management of neuropathic pain from all causes.

https://www.bmj.com/content/381/bmj.p866

Met dank aan dr. Leslie Vander Ginst

ISCHIAS: OPERATIEF VERSUS CONSERVATIEF BEHANDELEN?

Abstract

Objective To investigate the effectiveness and safety of surgery compared with non-surgical treatment for sciatica.

Design Systematic review and meta-analysis.

Data sources Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and the World Health Organisation International Clinical Trials Registry Platform from database inception to June 2022.

Eligibility criteria for selecting studies Randomised controlled trials comparing any surgical treatment with non-surgical treatment, epidural steroid injections, or placebo or sham surgery, in people with sciatica of any duration due to lumbar disc herniation (diagnosed by radiological imaging).

Data extraction and synthesis Two independent reviewers extracted data. Leg pain and disability were the primary outcomes. Adverse events, back pain, quality of life, and satisfaction with treatment were the secondary outcomes. Pain and disability scores were converted to a scale of 0 (no pain or disability) to 100 (worst pain or disability). Data were pooled using a random effects model. Risk of bias was assessed with the Cochrane Collaboration's tool and certainty of evidence with the grading of recommendations assessment, development, and evaluation (GRADE) framework. Follow-up times were into immediate term (≤six weeks), short term (>six weeks and ≤three months), medium term (>three and <12 months), and long term (at 12 months).

Results 24 trials were included, half of these investigated the effectiveness of discectomy compared with non-surgical treatment or epidural steroid injections (1711 participants). Very low to low certainty evidence showed that discectomy, compared with non-surgical treatment, reduced leg pain: the effect size was moderate at immediate term (mean difference −12.1 (95% confidence interval −23.6 to −0.5)) and short term (−11.7 (−18.6 to −4.7)), and small at medium term (−6.5 (−11.0 to −2.1)). Negligible effects were noted at long term (−2.3 (−4.5 to −0.2)). For disability, small, negligible, or no effects were found. A similar effect on leg pain was found when comparing discectomy with epidural steroid injections. For disability, a moderate effect was found at short term, but no effect was observed at medium and long term. The risk of any adverse events was similar between discectomy and non-surgical treatment (risk ratio 1.34 (95% confidence interval 0.91 to 1.98)).

Conclusion Very low to low certainty evidence suggests that discectomy was superior to non-surgical treatment or epidural steroid injections in reducing leg pain and disability in people with sciatica with a surgical indication, but the benefits declined over time. Discectomy might be an option for people with sciatica who feel that the rapid relief offered by discectomy outweighs the risks and costs associated with surgery.

Systematic review registration PROSPERO CRD42021269997.

What is already known

Discectomy and other surgical procedures are widely used for the treatment of sciatica secondary to lumbar disc herniation

Guidelines recommend discectomy when non-surgical treatments are unsuccessful, and imaging features are consistent with sciatica

Evidence supporting surgical treatment for sciatica is uncertain; reviews have substantial limitations in literature coverage, population selection, and method

What this study adds

Very low to low certainty evidence suggests that discectomy was superior to non-surgical treatment or epidural steroid injections in reducing leg pain and disability in people with sciatica with a surgical indication, but benefits reduced over time

Discectomy might be considered an early management option in people who the benefits of early improvement in leg pain or disability outweigh the costs and potential risks

Discectomy might cause surgical related complications, but trials included in this review are likely underpowered to detect harms with low incidences (eg, wound infection, recurrent disc herniation, and persistent postsurgical pain)

https://www.bmj.com/content/381/bmj-2022-070730

Met editoriaal commentaar:

Does new evidence challenge a stepped care approach for all patients?

International guidelines for sciatica recommend a stepped care approach starting with conservative management (ie, physiotherapy and medication), escalating to steroid injections, then surgery when non-surgical treatment has failed or when major radicular weakness is present. Unfortunately, evidence on the effectiveness of both non-surgical and surgical options is uncertain.

In a linked paper, Liu and colleagues (doi:10.1136/bmj-2022-070730) report a methodologically sound and balanced systematic review and meta-analysis of 24 randomised clinical trials evaluating the evidence of surgical care for people with sciatica due to lumbar disc herniation. Their meta-analysis suggests that discectomy is statistically significantly superior to non-surgical treatment in reducing leg pain and disability. However, effects were moderate at best (10-20 point reduction on a 100 point scale), but mostly small (5-10 point reduction). The benefits of discectomy were only evident in the short to medium term, with no clinically meaningful effects beyond 12 months.

Studies that evaluated plasma disc decompression and chemonucleolysis were also included, but the small number did not permit firm recommendations. Commendably, the authors carefully rated the certainty of evidence, which was low or very low. The true effect could, therefore, be markedly different from the reported estimates, allowing only weak clinical recommendations. This certainty of evidence is disappointing considering that 11 of the 12 trials evaluating discectomy were reported after the CONSORT reporting guidelines were published. The authors concluded that “discectomy might be an option for people with sciatica who feel that the rapid relief offered by discectomy outweighs the risks and costs associated with surgery.”

So, does that mean that people with sciatica should be offered surgery because they will experience more rapid improvements in pain and disability compared with non-surgical interventions? As always, context is key when interpreting study findings. In this systematic review, although not specifically mentioned by the research authors, most of the trials that examined the effect of discectomy recruited patients from secondary care. According to the stepped care approach recommended by international guidelines, secondary care referral should only be initiated for people who have not responded to conservative care or have severe

radicular weakness. Furthermore, to be considered for surgery, patients require a surgical indication such as a structural target on magnetic resonance imaging (MRI). Accordingly, this systematic review included only trials of people with discogenic sciatica diagnosed by MRI. However, only 30% of patients in secondary care have an MRI finding that matches the spinal level predicted by clinical examination and thus represents a clear surgical indication.The results of this systematic review therefore relate to a much smaller and more defined group than the heterogeneous population with sciatica encountered in community healthcare settings.

In primary care, about two thirds of people with sciatica recover within two to three months without the need or even an indication for invasive treatments. Therefore, extrapolation of Liu and colleagues' findings to a primary care population would be misleading. Their conclusions should be limited to people with a specific diagnosis of radicular pain with or without radiculopathy, who have likely not responded adequately to non-surgical approaches, or to people with severe pain and a large enough impact on quality of life to warrant secondary care referral. A more appropriate conclusion might be that discectomy could be an option for people with radicular pain (with or without radiculopathy) who present to secondary care settings with a clear indication for surgery.

Despite limitations related to the low certainty of evidence, Liu and colleagues' review raises an important point for clinicians, people with sciatica, and policy makers. Growing evidence for worse surgical outcomes associated with prolonged symptom duration, together with the better short and medium term benefits of discectomy reported in this systematic review, challenge the stepped care approach that offers the least invasive options first to everyone with sciatica. Expedited surgical triage would be preferable for people with discogenic sciatica and a clear indication for surgery when rapid pain relief is a priority. Although many international pathways have this intention, reality is often divergent. Access to specialist services is difficult and delayed in many health systems globally, requiring proactiveness and perseverance from the patient, which is often compromised by their symptoms. Easier and faster access to surgical triage is needed for patients who are most likely to benefit.

Although the new review cannot provide clear treatment recommendations, the findings highlight one of the main obstacles to improving outcomes in this clinical field: sciatica is a heterogeneous condition and no routine clinical measures can consistently predict outcome. This knowledge gap hinders early triage, including to more invasive treatments. Solving the heterogeneity puzzle is the key to helping people with sciatica and clinicians choose the right treatment for them earlier in the disease trajectory, while being fully informed of the benefits and risks of surgery.

https://www.bmj.com/content/381/bmj.p791

Met dank aan dr. Leslie Vander Ginst

EPICONDYLITIS LATERALIS OFTE TENNIS ELLEBOOG

What you need to know

Symptoms of lateral epicondylitis usually resolve within one year with activity modification and watchful waiting

Current evidence suggests that steroid injections do not offer long term benefit

Secondary care management may include percutaneous needle fenestration or injections of autologous blood or platelet rich plasma; however, evidence of moderate certainty shows no benefit from these treatments

Surgical management in refractory cases usually involves open or arthroscopic release of the affected muscle tendon

Lateral epicondylitis (also known as tennis elbow) is a common, often debilitating disorder frequently encountered in primary care across low and high resource settings. This article outlines current management strategies, including supportive measures, activity modification, and newer treatments that have emerged over the past 20 years, such as percutaneous needle fenestration and injection of autologous blood and platelet rich plasma.

What is lateral epicondylitis?

Lateral epicondylitis is a type of tendinosis, a degenerative process where repetitive stress causes fibroblast deposition with collagen disorganisation and vascular hyperplasia. Pain causes underuse of the affected arm and further weakening in the tendon structure, with possible sequelae of partial or complete rupture of the tendon. Cadaveric and electromyographic studies show that symptoms (namely, lateral elbow pain) are often related to excessive loading of the lateral extensor tendons, as well as repetitive wrist extension or supination movements. The condition commonly presents as a work related strain injury, and often affects tennis players6 (box 1).

Box 1

Who gets it?

- Incidence of lateral epicondylitis is 1.5 to 2.4 cases per 1000 people, according to research from the US. Most population studies have been carried out in high resource settings.
- Occupational exposure can predispose to development of tendinopathy. Lateral epicondylitis is more prevalent in people whose profession involves manual work, with a particular link to forceful or repetitive movements.
- Incidence is higher in people of working age, with peaks at ages 40 to 50.
- Steroid use and smoking history are risk factors.
- The condition has been linked to other problems of the upper limb, such as rotator cuff pathology, de Quervain disease, and carpal tunnel syndrome.

How is it diagnosed?

Lateral epicondylitis is a clinical diagnosis. Patients usually present to primary care describing pain at the lateral aspect of the elbow and radiating down the forearm to the wrist. Initial stages present similarly to muscle strain, but can progress to involve the tendon, causing more severe pain. Most people experience symptoms when using their forearm or wrist only, although in some patients, the pain is persistent and occurs at night, leading to sleep disturbance. Box 2 lists differential diagnoses.

Box 2

Differential diagnoses

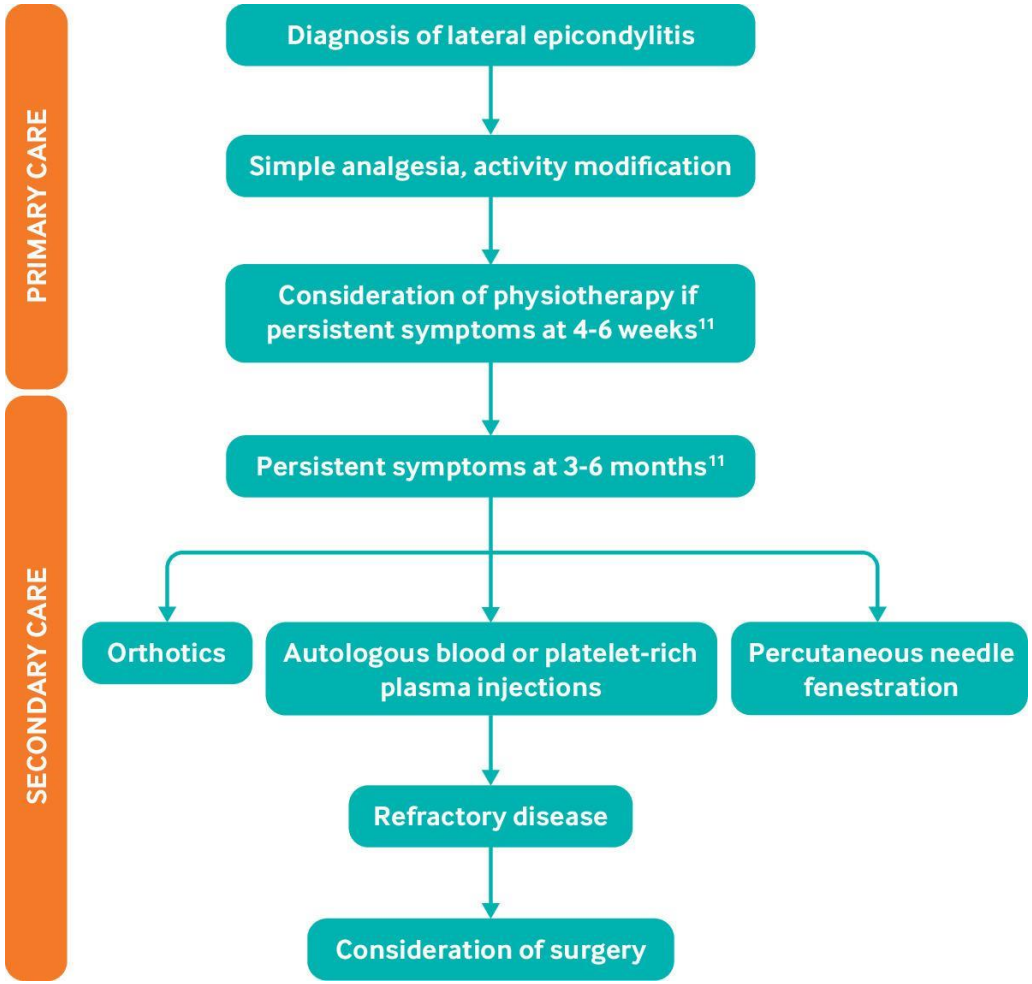
- Radial tunnel syndrome—posterior interosseous nerve compression causing pain on the posterolateral aspect of the arm. It may be worse at night and associated with weakness on wrist or finger extension
- Arthropathy—osteoarthritis in the elbow commonly affects the radiocapitellar joint, and can lead to loss of range of motion
- Elbow plica—synovial fold causes lateral elbow pain. Patients can experience clicking or locking during elbow motion
- Referred pain from cervical radiculopathy—can be associated with neck pain and arm numbness or weakness in relevant dermatomes or myotomes
- Referred pain from shoulder pathology—elbow pain can be caused by overuse to compensate for limited ipsilateral shoulder function
- Osteochondritis dissecans—usually in younger patients, more common in gymnasts and throwers, and often associated with swelling or locking of the joint
- Synovitis—inflammation of the membrane surrounding the joint, causing pain which is associated with swelling, warmth, or stiffness
- Trauma—new or old injury resulting in fractures, loose bodies, or chondral lesions
- Infection and inflammatory arthritis—heat, redness, and swelling on examination
- Malignancy—rare; may present with palpable mass on examination, night pain, constitutional symptoms

Lateral epicondylitis can be extremely debilitating, affecting all daily activities. Grip strength is often reduced because of pain, and many patients find it difficult to use cutlery or lift household objects. While range of motion is not usually affected, patients can experience stiffness, which is likely secondary to pain and underuse of the affected limb.

What is the natural progression?

Lateral epicondylitis is generally considered to be a self-limiting condition; however, its course is poorly described in literature. One systematic review of 24 randomised controlled trials (RCTs) looking at patients who received placebo or no treatment described symptom resolution at one year in 90% of individuals, with most experiencing improvement in the first three to six months from onset. In some case reports, the pain had been persistent for more than two years. Recurrence is uncommon, with one population study estimating the overall recurrence rate at 8.5% with median time to recurrence of 19.7 months.

Fig. 1: Proposes treatment algorithm for patients with diagnosis of lateral epicondylitis



Watchful waiting

Current guidelines from the Canadian Shoulder and Elbow Society and NICE recommend having a discussion with the patient about trialling a "watchful waiting" approach in the first instance. In line with NICE guidance,we suggest the following:

Offer patients advice on rest and avoidance of painful movements

Reassess the patient after three to six months to determine the next course of action

Consider a trial of activity modification, particularly in the workplace setting, for patients who rely on manual work

Consider patient preference regarding when to refer to physiotherapy or secondary care.

A 2021 systematic review and meta-analysis of 17 randomised studies, with median follow-up of 12 months, showed no statistically significant difference in functional and pain outcomes between patients who received no active treatment and those who received non-operative management, including physiotherapy, steroid injections, platelet rich plasma, and autologous blood.

Simple analgesia

Offer all patients advice on simple analgesia for short term relief, with the aim of supporting them to continue their activities of daily living. Consider using the World Health Organization's analgesic ladder to guide treatment escalation. The evidence underlying this is limited, with a 2013 Cochrane review finding low quality evidence to suggest efficacy of topical non-steroidal anti-inflammatory drugs (NSAIDs) in reducing pain compared with placebo for up to four weeks, and inconclusive evidence regarding the ability of oral NSAIDs and long term use of NSAIDs to affect the natural progression of the condition.

Physiotherapy

No universal programme of physiotherapy exists for lateral epicondylitis; however, consider referral to a physiotherapist if symptoms have not eased after four to six weeks.

Exercise is usually used as an adjunct to other therapies, and programmes may consist of two to three sessions a week for a period of six to eight weeks.

Two RCTs in Australia (2013 and 2006) assessed short and long term efficacy of physiotherapy treatment compared with no treatment in patients with a six week history of lateral epicondylitis. In one, patients who underwent physiotherapy had improved grip strength and functional and pain scores compared with watching and waiting at six weeks, but in both studies, rates of recovery of symptoms at one year were similar, suggesting no clear advantage in treatment with physiotherapy in the medium or long term. In contrast, a 2021 systematic review and meta-analysis of 2123 participants in 30 RCTs showed a small but clinically significant improvement in pain-free grip strength in patients receiving physiotherapy, compared with passive interventions, in the short and mid-term (<12 months) and long term follow-up >12 months.

Online guides and videos suggest exercises to do at home (eg, from the British Elbow and Shoulder Society). Evidence regarding technique-specific exercises is outlined below:

Gripping tasks and exercises targeting extensor muscles may improve pain levels and rates of return to work, according to evidence from prospective studies in Australia and Canada.

Eccentric strengthening (such as slowly bending the wrist against resistance) is superior to other exercise regimens with respect to pain levels

and functional scores, according to evidence from a 2021 systematic review and meta-analysis. Similarly, in one small RCT involving 20 patients in India, a supervised programme of stretches and eccentric strengthening led to an improvement in pain score and function compared with manual therapy (friction massage and joint manipulation).

Corticosteroid injections

Up until the past decade, corticosteroid injections—typically a single injection, usually mixed with local anaesthetic around the symptomatic area—were commonly used in managing initial symptoms that had not improved by four to six weeks from onset. Over the past 10 years, however, evidence has shown that, while corticosteroid injections may provide short term symptom relief, the effects may wane longer term:

In the 2013 RCT including 165 patients in Australia, corticosteroid injections were associated with lower recovery rates at one year compared with no treatment (83% versus 96%, P=0.01). Recovery rates between patients receiving corticosteroid injections only and corticosteroid injections with physiotherapy were similar.

In the 2006 RCT involving 198 patients in Australia, corticosteroid injections were found to be superior to multiple non-operative strategies, with respect to grip strength and functional and pain scores at six weeks.At one year, however, many participants experienced recurrence of pain with inferior outcome scores compared with physiotherapy.

In a 2021 systematic review, corticosteroid injections were found to be associated with worse functional and pain scores compared with no active treatment at 6-12 months' follow-up.

In a 2002 RCT involving 185 patients in the Netherlands, higher rates of lateral epicondylitis recurrence at one year were noted in patients receiving corticosteroid injections compared with patients receiving physiotherapy or a watchful waiting approach.

Side effects of corticosteroid injections

Several side effects are associated with use of corticosteroid injections, although these are usually minor and tend to resolve within six months of starting treatment. They include persistent pain after injection, loss of skin pigment (5%), and tissue atrophy at injection site (4%). Administration of steroids can also induce hyperglycaemia, particularly in patients with diabetes mellitus.

Acupuncture

In several countries, acupuncture has been used as an alternative treatment; however, evidence to support its use is insufficient, and current RCT data on whether it can provide sustained pain relief remain inconclusive.

Is imaging required?

Imaging is not always required for diagnosis; however, ultrasound or magnetic resonance imaging may be considered in secondary care to confirm the diagnosis.

When is specialist assessment required?

No particular timeframe is recommended for referral to a specialist. However, if symptoms persist after six months of community treatment, consider arranging assessment by an orthopaedic surgeon or a sports medicine physician.

What secondary care management options are available?

Orthotics

Some high quality evidence supports the use of orthotics to alter the force vectors across the tendon and offload the area of diseased tendon tissue.

In a 2009 randomised crossover study of 52 patients in Iran, epicondylar braces were shown to improve pain-free grip strength.

A 2019 RCT involving 31 patients in Australia showed that counterforce bracing was associated with improvement in pain levels and function, compared with a placebo brace.

A 2018 RCT, involving 82 patients in Turkey, compared hand-wrist resting orthosis with an epicondylitis bandage, and found good improvement in the first six weeks of use in terms of pain and function and grasp strength in both groups. No statistically significant differences in outcomes were noted between the two approaches.

Two recent systematic reviews, however, suggested that, compared with orthoses, other treatment modalities including physiotherapy may be associated with more favourable outcomes, particularly long term. Age of patient and goal of treatment, such as short term alleviation of pain, were relevant covariates.

Autologous blood injections and platelet rich plasma injections

Injections of autologous blood and platelet rich plasma have become increasingly popular in high resource settings in the past 20 years. Samples are collected from the patient and injected around the lateral epicondyle to trigger an inflammatory reaction and facilitate tendon recovery with cellular mediators. Most patients receive a single injection, although courses of two injections separated by two to four weeks have been instituted in some regimens.

Some early studies reported encouraging outcomes for platelet rich plasma, and some clinicians now use them as an alternative to steroid injections or surgery. However, evidence from subsequent RCTs showed no benefit of routine use of either injections.

A 2021 Cochrane systematic review assessing 32 studies with 2337 participants and another systematic review of five RCTs showed no benefit of either injection compared with no treatment or placebo at three months and six months or more. The reviews assessed multiple outcomes, including pain relief, function, quality of life, and withdrawal.

A 2013 RCT involving 60 patients in Denmark noted no difference in pain scores between corticosteroid injections, platelet rich plasma injections, and placebo at three months.

Some studies have described superior outcomes in the platelet rich plasma injections group compared with autologous blood injections, but overall no difference is seen between the two injections: a 2014 RCT of 76 patients in Iran showed no difference in pain and functional scores between both injections, in the short or long term, with 12 month follow-up, which is supported by the 2021 Cochrane review of four trials that also highlight the additional costs associated with the centrifugation process used to obtain platelet rich plasma.

Transient pain at the injection site has been reported to occur in up to 20% of patients receiving these treatments. One systematic review noted that injection of autologous blood was associated with lower rates of discomfort compared with platelet rich plasma.

Percutaneous needle fenestration

Percutaneous needle fenestration (piercing the damaged part of the tendon with a needle) may be performed under local anaesthetic with or without ultrasound guidance. It is often carried out in conjunction with platelet rich plasma or autologous blood injections. The overall quality of evidence of this treatment in isolation is low and it is currently uncertain whether it is more effective than conservative treatment or placebo.

Shockwave therapy

Shockwave therapy is used for various tendinopathies, particularly in higher resource settings. Evidence to support its effectiveness in

treating lateral epicondylitis is currently inconclusive; however, results from small RCTs suggest that it may be associated with reduced pain levels and improved grip strength compared with placebo.

Laser therapy

A 2008 systematic review and meta-analysis of 18 RCTs concluded that, at certain therapeutic wavelengths, laser therapy could lead to short term improvement in pain relief and improved function, with no reported side effects. However, the overall benefit of this labour intensive treatment compared with other non-operative strategies, or no treatment, remains uncertain.

Surgery

Surgery may be considered in cases where symptoms do not improve with other therapies. A 2018 epidemiological study from the US of insurance records estimated the percentage of patients with lateral epicondylitis who go on to require any surgery (including fasciotomy, tenotomy, or debridement) as 2%.

No recommendations are available on the timeframe for when to offer surgical treatment, and currently little evidence supports the persistence of symptoms as an indication for surgery to compare the effectiveness of surgery and non-operative treatments, or to determine the optimal surgical technique.

While short term symptom improvement has been noted, this is likely in line with natural progression of the condition, and one study found mean duration of postoperative symptoms was 2.2 years with open debridement. Similarly, a small 2018 RCT41 comparing open resection with placebo surgery showed no difference between the two.

Arthroscopic and percutaneous techniques are less invasive alternatives to open surgery, with some evidence showing similar or superior outcomes with respect to patient satisfaction and recovery, compared with more established open surgery. Arthroscopic techniques may offer the benefit of identifying other elbow pathologies that can be simultaneously treated. Further large scale studies, ideally randomised controlled trials, are needed to assess the potential benefits of surgery in patients for whom non-operative interventions have led to refractory disease.

https://www.bmj.com/content/381/bmj-2022-072574

Met dank aan dr. Leslie Vander Ginst

Palliatieve zorg

DEZE ZORG BESTRIJKT EEN VEEL BREDERE REGIO DAN VAAK GEDACHT

Deze zorg beperkt zich niet enkel tot terminale zorg, maar wordt bij alle levensbedreigende aandoeningen of kwetsbaarheid tijdig opgestart.

Definitie in Nederland:
'Zorg die de kwaliteit van het leven verbetert van patiënten en hun naasten die te maken hebben met een levensbedreigende aandoening of kwetsbaarheid door het voorkomen en verlichten van lijden, door middel van vroegtijdige signalering en zorgvuldige beoordeling en behandeling van problemen van fysieke, psychische, sociale en spirituele aard'.

Enkele cijfers:
- Er is toenemende aandacht voor palliatieve zorg in de afgelopen jaren:
  - Er stierven in Nederland in 2018 en 2019 ongeveer 152.000 mensen.
  - De sterfte liep in Nederland mede door de covid-19-epidemie in 2020 op tot ongeveer 170.000 mensen per jaar.
- 72-75% van de mensen die overlijden komen naar schatting in aanmerking voor palliatieve zorg.
- In deze groep zijn de meest voorkomende doodsoorzaken kanker, hartaandoeningen, dementie en covid-19 (in 2020).

Waarop kan palliatieve zorg zich richten ?
- Kan zich zowel op de onderliggende ziekte – ziektegerichte palliatie – als op klachten en problemen – symptoomgerichte palliatie – richten:
  - De mogelijkheden van ziektegerichte palliatie nemen in de loop van de tijd over het algemeen af.
  - In alle fasen van het ziekteproces blijft adequate symptoomcontrole van groot belang.
- Palliatie in de stervensfase richt zich op kwaliteit van sterven, en nazorg voor de naasten is ook onderdeel van palliatieve zorg.
- Palliatieve zorg omvat dus veel meer dan terminale zorg.

De palliatieve fase:
- Wanneer de palliatieve fase juist opstart, hangt af van de onderliggende ziekte:
  - In het geval van kanker start de palliatieve fase als de kanker ongeneeslijk is of geworden is.
  - De palliatieve fase begint bij ongeneeslijke ziekten die altijd tot de dood leiden, type ALS, bij de diagnosestelling.
- Het ziektebeloop en de afloop zijn bij kwetsbaarheid en bij chronische ziekten, zoals COPD en hartfalen, onzekerder en hier is de 'surprise question' behulpzaam voor de markering van de palliatieve fase:
  - 'Zou u verbaasd zijn als uw patiënte binnen een jaar overleden is?'
  - Is het antwoord nee, dan wordt de palliatieve fase gemarkeerd.
- Mede afhankelijk van de onderliggende aandoening kan de palliatieve fase qua duur variëren van dagen tot jaren:
  - De keuze bij diagnostiek en behandeling wordt in hoge mate bepaald door de geschatte levensverwachting.
  - Aan de behandelende arts is het om in samenspraak met de patiënt deze keuzes te maken.
- Met een scala aan klachten en problemen worden patiënten in de palliatieve fase geconfronteerd:
  - Dat geldt niet enkel op lichamelijk vlak.
  - Geldt ook op psychisch, sociaal en spiritueel gebied.
- Men gebruikt voor de term 'spiritueel' ook wel de term 'existentieel', maar conform het kwaliteitskader ' Palliatieve zorg Nederland' wordt in dit artikel verder de term 'spiritueel' gebruikt.

- Palliatieve zorg vereist expertise en een interdisciplinaire benadering:
  - Men bedoelt hiermee dat niet alleen meerdere disciplines betrokken zijn (multidisciplinair).
  - Deze werken ook onderling samen en stemmen de zorg op elkaar af.
- Volgen in dit artikel een aantal belangrijke aspecten van palliatieve zorg.

'Later begint vandaag':

- Het is van belang om tijdig te weten wat iemand wel of juist niet wil aan zorg om dan goede en passende zorg te verlenen:
  - De zorg wordt afgestemd op persoonlijke wensen, waarden en behoeften door behandelwensen en -grenzen gezamenlijk te bespreken en vast te leggen.
  - Internationaal wordt proactieve zorgplanning – 'advance care planning' – gedefinieerd als de mogelijkheid voor individuen om persoonlijke doelen en voorkeuren voor toekomstige medische behandeling en zorg te bepalen, te bespreken met naasten en zorgverleners, vast te leggen en zo nodig te herzien.
  - Bij voorkeur wordt het gesprek voor het eerst aan het begin van de palliatieve fase gevoerd.
- Er kunnen ook andere aanleidingen zijn: op initiatief van de patiënt, verwachte werkonbekwaamheid in de toekomst, frequente ziekenhuisopnames, optreden van complicaties of verslechtering va n de algemene toestand:
  - Men kijkt hiervoor best ook naar de desbetreffende modules van de richtlijnen over palliatieve zorg bij COPD, hartfalen, nierfalen, ALS en dementie.
  - Men kan de wensen ook vastleggen in een schriftelijke wilsverklaring.
- Als de gezondheidstoestand van de patiënt verandert wordt het gesprek opnieuw gevoerd:
  - Kan ook gebeuren als de patiënt of diens vertegenwoordiger erom vraagt.
  - Zo nodig wordt de wilsverklaring dan aangepast.
- Het gesprek kan gevoerd worden door verschillende zorgverleners: kan gaan om artsen, verpleegkundigen en verpleegkundig specialisten, physician assistants en praktijkondersteuners.
- Niet alleen maar (niet-)behandelbesluiten en beslissingen rond het levenseinde komen in dit gesprek aan bod, maar ook ander zaken:
  - Kan gaan om individuele levensdoelen, doelen van de zorg, gewenste plaats van zorg en sterven en hoe te handelen in crisissituaties en bij ziekenhuisopnames.
  - Kan ook gaan om het aanwijzen van een vertegenwoordiger, het opstellen van een wilsverklaring, wensen met betrekking tot de uitvaart en dergelijke.
- Patiënten kan men wijzen op de informatie op thuisarts.nl.

Niet alleen ongeneeslijke kanker:

- Er zijn heel wat patiënten, maar ook sommige zorgverleners, die onvoldoende stilstaan bij de volgende bedenking:
  - De prognose van een gevorderd stadium van bepaalde aandoeningen kan even kort of zelfs korter zijn dan de prognose van patiënten met ongeneeslijke kanker.
  - Gaat bvb. om COPD, hartfalen, nierfalen of neurodegeneratieve aandoeningen zoals ALS en de ziekte van Parkinson.
  - Soms is de kwaliteit van leven nog slechter.
- Dat er nog weinig aandacht is voor palliatieve zorg en gesprekken over het levenseinde bij patiënten met een niet-oncologische aandoening in een gevorderd stadium is het gevolg hiervan.
- De richtlijnen voor palliatieve zorg bij COPD, hartfalen, nierfalen, ALS, dementie en de ziekte van Parkinson kunnen geraadpleegd worden op palliaweb.nl.

Niet enkel aandacht voor het lichamelijke:

- De vier dimensies – lichamelijk, psychisch, sociaal en spiritueel – komen in de definitie van palliatieve zorg expliciet aan de orde:

- Ze zijn in de praktijk sterk met elkaar verweven.
- Een voorbeeld hiervan is het begrip ‘total pain’.

- Men spreekt van total pain als psychische, sociale of spirituele factoren een sterke invloed hebben op de pijn.
- De pijnbeleving en het pijngedrag worden bepaald door het samenspel van de vier dimensies:
  - Ieder symptoom vraagt om multidimensionele benadering.
  - Spelen psychosociale of spirituele factoren een belangrijke rol, dan sorteert een behandeling die uitsluitend op de lichamelijke dimensie gericht is onvoldoende effect.
- Het spirituele domein is niet aan geestelijke verzorgers voorbehouden:
  - De richtlijn ‘Zingeving en spiritualiteit in de palliatieve fase’ geeft handvatten aan zorgverleners om hierover in gesprek te gaan.
  - Voor artsen en andere zorgverleners is de grootste valkuil hierbij hun oplossingsgerichte benadering.
  - In dit domein zijn oplossingen meestal niet voorhanden en een luisterend oor – presentie volstaat.

Zorgvuldige analyse:

- De basis van een goede palliatieve zorg is een zorgvuldige analyse van symptomen bij patiënten in de palliatieve fase:
  - Hierbij hoort aandacht voor de vier bovengenoemde dimensies.
  - Er is ook aandacht vereist voor de impact van deze dimensies op de kwaliteit van leven.
- Factoren die bij de analyse aan bod komen:
  - Medische voorgeschiedenis, comorbiditeit en ingeschatte levensverwachting.
  - Huidige medicatie en symptoomanalyse door middel van anamnese en lichamelijk onderzoek.
  - Betekenisgeving, prioriteiten en wensen van de patiënt.
- Men kan hierbij eventueel gebruik maken van meetinstrumenten:
  - Het Utrechts Symptoom Dagboek (USD) is hiervan een voorbeeld.
  - Hierin worden een aantal veelvoorkomende symptomen in de palliatieve fase gescoord met een ‘numeric rating scale’.
- Wanneer dat zinvol en passend is, kan men aanvullende diagnostiek verrichten:
  - Dit gebeurt dan in het licht van de aard van de klachten, de setting thuis, verpleeghuis of hospice versus ziekenhuis, de levensverwachting en de wensen van de patiënt.
  - Nadien worden er werkhypotheses geformuleerd, waarin de mogelijke oorzaken en beïnvloedende factoren voor ieder symptoom benoemd worden.
- Men stelt dan aan de hand van de werkhypotheses een behandelplan op met aandacht voor een aantal factoren:
  - Als het mogelijk is een behandeling van de oorzakelijke en beïnvloedende factoren, bvb. de behandeling van hypercalciëmie als oorzaak van misselijkheid of behandeling van angst als dat een belangrijke rol speelt bij pijn.
  - Niet-medicamenteuze symptomatische behandeling, bvb. een ontlastende punctie bij klachten als gevolg van ascites.
  - Medicamenteuze symptomatische behandeling , bvb. morfine bij dyspnoe.
- Er worden afspraken gemaakt over de evaluatie van het effect later, wanneer er met een behandeling gestart wordt:
  - Door wie, hoe en wanneer.
  - De behandeling wordt aan de hand van het effect eventueel bijgesteld.

Informatie en advies:

- Begeleiding van een patiënt in de palliatieve fase gebeurt bij vele verzorgers maar af en toe, wat maakt dat ze relatief weinig ervaring hebben in en met palliatieve zorg:

- In de studie geneeskunde en de diverse opleidingen is er bovendien nog heel weinig aandacht voor palliatieve zorg.
- Deskundigheid kan daardoor soms tekortschieten, en zeker in complexe situaties.

- Er is gelukkig veel informatie beschikbaar, zoals diverse richtlijnen en handreikingen, Palliaweb, de PalliArts-app en hulpmiddelen voor artsen bij gesprekken over het levenseinde.
- Er is bovendien de mogelijkheid voor consultatie van experts palliatieve zorg:
  - Men kan in iedere regio in Nederland 24/7 een expert raadplegen, meestal telefonisch.
  - Er bestaat hiervoor één landelijk telefoonnummer dat via de postcode van de consultvrager bij een consultatieteam uitkomt.
- Consultatie kan bij een in een ziekenhuis opgenomen patiënt – vaak ook 'bedside' – gevraagd worden van een intra- of transmuraal palliatief team.

Niet alles wat kan, hoeft:

- De mogelijkheden voor ziektegerichte behandeling worden steeds groter, en dat geldt ook in de palliatieve fase:
  - Geldt niet alleen voor patiënten met kanker, maar ook voor patiënten metniet-oncologische aandoeningen.
  - De afweging van baten en lasten kan moeilijk vallen.
  - Het kan bovendien voor zowel zorgverleners als patiënten moeilijk zijn om met de behandeling te stoppen of om af te zien van (nieuwe) behandelingen.
- Gevolg is dat behandelingen nogal eens met te veel bijwerkingen en belasting gepaard gaan en dat er te lang doorbehandeld wordt.
- Door de behandeling wordt de kwaliteit van leven dan in negatieve zin beïnvloed.
- Dat zowel huisartsen als medisch specialisten met elkaar en met de patiënt over de zin van het beginnen of voortzetten van belastende behandelingen in gesprek gaan is essentieel:
  - De voor- en nadelen van de behandeling worden hierbij op een rijtje gezet.
  - Het afzien of stoppen van behandeling moet niet expliciet of impliciet als 'niets doen' gebracht worden.
- Men moet de term 'uitbehandeld' nooit gebruiken, want daarmee legt men het accent op de ziektegerichte behandeling, en gaat men voorbij aan de mogelijkheden van palliatieve behandeling.

Omgaan met een doodswens:

- Kan in het kader van een levensbedreigende ziekte ontstaan, maar ook in de context van kwetsbaarheid of een stapeling van ouderdomsverschijnselen.
  - Zo'n wens vraagt een zeer zorgvuldige analyse van de factoren die aan de grondslag liggen.
  - Vraagt om een analyse van de mogelijkheid tot behandeling ervan.
- Euthanasie of hulp bij zelfdoding kan bij een doodswens een optie zijn:
  - Kan gebeuren als dat een wens van de betrokkene is.
  - Kan gebeuren als er voldaan wordt aan de zorgvuldigheidseisen.
  - De behandelaar is ten slotte bereid om de euthanasie uit te voeren.
- Bewust stoppen met eten en drinken is een alternatief om hierdoor te komen overlijden:
  - Men moet hierbij niet voldoen aan de zorgvuldigheidseisen.
  - Patiënt is bovendien niet afhankelijk van een zorgverlener om de interventie uit te voeren.
  - Eet en drinkt de patiënt niet consequent, dan komt deze meestal binnen 1-2 weken te overlijden.
- Bij gesprekken over het levenseinde of een actuele doodswens is bewust stoppen met eten en drinken een optie.

Tijdig herkennen van de naderende dood:

- Aan de hand van klinische observaties van zowel arts als verpleegkundige wordt de stervensfase gemarkeerd:
  - Een relatief plotse achteruitgang ('een knik in de lijn').

- Niet of nauwelijks meer eten en drinken / zwakte en bedlegerigheid.
- Tekens van verminderde circulatie: zwakke of afwezige pols / verkleuring van de huid: marmering, circulatievlekken / koude acra, zwakke tot afwezige pols / verminderde tot afwezige urineproductie / verminderd bewustzijn.

- Bij voorkeur wordt de stervensfase gemarkeerd alvorens late symptomen van de stervensfase optreden, zoals reutelen, terminaal delier of cheyne-stokesademhaling.
- Tijdige markering van de stervensfase creëert duidelijkheid:
  - Kan voor de patiënt de naasten tot meer rust leiden.
  - Geeft tijd voor afronding en afscheid nemen.
  - Draagt bij aan betere rouwverwerking van de naasten.
  - Heeft ook effect op de kwaliteit van de zorg en plaats van overlijden.
  - Geeft ook vermindering van diagnostiek en medische en verpleegkundige interventies.
  - Voor de communicatie tussen de zorgverleners onderling en tussen de zorgverleners en de patiënt en diens naasten is dit ook belangrijk.
- De focus van de zorg ligt dan op de kwaliteit van sterven:
  - Over het stervensproces en wat te verwachten valt worden patiënten en naasten geïnformeerd.
  - Onnodige medische en verpleegkundige interventies worden gestaakt.
  - De medicatie wordt tot het strikt noodzakelijke beperkt en de toedieningsweg wordt zo nodig aangepast.
  - De patiënt of een naaste krijgt de beschikking over medicatie voor acute verergering van klachten.

Besluit:

- Bij palliatieve zorg gaar het dus niet enkel om patiënten met kanker, maar ook om patiënten met andere chronische aandoeningen, zoals bvb. COPD, hart- en nierfalen, en om kwetsbare patiënten.
- Wat vraagt optimale palliatieve zorg ?
  - Kennis, communicatieve vaardigheden en een juiste attitude.
  - Een systematische benadering van alle klachten en problemen.
  - Aandacht voor alle dimensies: lichamelijk, psychisch, sociaal en spiritueel.
  - Interdisciplinaire samenwerking.
- Het is van belang om te anticiperen op vragen en problemen die zich kunnen voordoen in de toekomst.
- Aanvankelijk is de zorg gericht op kwaliteit van leven:
  - Men zoekt daarbij naar een goede balans tussen ziektegerichte en symptoomgerichte behandeling.
  - De focus verschuift in de stervensfase naar kwaliteit van sterven.

Ned Tijdschr Geneeskd 30 november 2023 pag. 48-54.

Met dank aan dr. Willy Storms

BIPOLAIRE AANDOENINGEN: EEN OVERZICHT

Introduction

Abnormal states of mood, ranging from excesses of despondency, psychic slowness, diminished motivation, and impaired cognitive functioning on the one hand, and exhilaration, heightened energy, and increased cognitive and motoric activity on the other, have been described since antiquity. However, the syndrome in which both these pathological states occur in a single individual was first described in the medical literature in 1854, although its fullest description was made by the German psychiatrist Emil Kraepelin at the turn of the 19th century. Kraepelin emphasized the periodicity of the illness and proposed an underlying trivariate model of mood, thought (cognition), and volition (activity) to account for the classic forms of mania and depression and the various admixed presentations subsequently know as mixed states. These initial descriptions of manic depressive illness encompassed most recurrent mood syndromes with relapsing remitting course, minimal interepisode morbidity, and a wide spectrum of “colorings of mood” that pass “without a sharp boundary” from the “rudiment of more severe disorders…into the domain of personal predisposition.” Although Kraepelin’s clinical description of bipolar disorder (BD) remains the cornerstone of today’s clinical description, more modern conceptions of bipolar disorder have differentiated manic depressive illness from recurrent depression, partly based on differences in family history and the relative specificity of lithium carbonate and mood stabilizing anticonvulsants as anti-manic and prophylactic agents in bipolar disorder. While the boundaries of bipolar disorder remain a matter of controversy, this review will focus on modern clinical conceptions of bipolar disorder, highlighting what is known about its causes, prognosis, and treatments, while also exploring novel areas of inquiry.

Modern definitions of bipolar disorder

In the 1970s, the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders reflected the prototypes of mania initially described by Kraepelin, following the “neo-Kraepelinian” model in psychiatric nosology. To meet the primary requirement for a manic episode, an individual must experience elevated or excessively irritable mood for at least a week, accompanied by at least three other typical syndromic features of mania, such as increased activity, increased speed of thoughts, rapid speech, changes in esteem, decreased need for sleep, or excessive engagement in impulsive or pleasurable activities. Psychotic symptoms and admission to hospital can be part of the diagnostic picture but are not essential to the diagnosis. In 1994, Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) carved out bipolar disorder type II (BD-II) as a separate diagnosis comprising milder presentations of mania called hypomania. The diagnostic criteria for BD-II are similar to those for bipolar disorder type I (BD-I), except for a shorter minimal duration of symptoms (four days) and the lack of need for significant role impairment during hypomania, which might be associated with enhanced functioning in some individuals. While the duration criteria for hypomania remain controversial, BD-II has been widely accepted and shown to be as common as (if not more common than) BD-I.6 The ICD-11 (international classification of diseases, 11th

revision) included BD-II as a diagnostic category in 2019, allowing greater flexibility in its requirement of hypomania needing to last several days.

The other significant difference between the two major diagnostic systems has been their consideration of mixed symptoms. Mixed states, initially described by Kraepelin as many potential concurrent combinations of manic and depressive symptoms, were more strictly defined by DSM as a week or more with full syndromic criteria for both manic and depressive episodes. In DSM-5, this highly restrictive criterion was changed to encompass a broader conception of subsyndromal mixed symptoms (consisting of at least three contrapolar symptoms) in either manic, hypomanic, or depressive episodes. In ICD-11, mixed symptoms are still considered to be an episode, with the requirement of several prominent symptoms of the countervailing mood state, a less stringent requirement that more closely aligns with Kraepelin's broader conception of mixed states.

Epidemiology

Using DSM-IV criteria, the National Comorbidity Study replication found similar lifetime prevalence rates for BD-I (1.0%) and BD-II (1.1%) among men and women. Subthreshold symptoms of hypomania (bipolar spectrum disorder) were more common, with prevalence rate estimates of 2.4%. Incidence rates, which largely focus on BD-I, have been estimated at approximately 6.1 per 100 000 person years (95% confidence interval 4.7 to 8.1). Estimates of the incidence and lifetime prevalence of bipolar disorder show moderate variations according to the method of diagnosis (performed by lay interviewers in a research context v clinically trained interviews) and the racial, ethnic, and demographic context. Higher income, westernized countries have slightly higher rates of bipolar disorder, which might reflect a combination of westernized centricity in the specific idioms used to understand and elicit symptoms, as well as a greater knowledge, acceptance, and conceptualization of emotional symptoms as psychiatric disorders.

Causes of bipolar disorder

Like other common psychiatric disorders, bipolar disorder is likely caused by a complex interplay of multiple factors, both at the population level and within individuals, which can be best conceptualized at various levels of analysis, including genetics, brain networks, psychological functioning, social support, and other biological and environmental factors. Because knowledge about the causes of bipolar disorder remains in its infancy, for pragmatic purposes, most research has followed a reductionistic model that will ultimately need to be synthesized for a more coherent view of the pathophysiology that underlies the condition.

Insights from genetics

From its earliest descriptions, bipolar disorder has been observed to run in families. Indeed, family history is the strongest individual risk factor for developing the disorder, with first degree relatives having an approximately eightfold higher risk of developing bipolar disorder compared with the baseline population rates of ~1%. While family studies cannot separate the effects of genetics from behavioral or cultural transmission, twin and adoption studies have been used to confirm that the majority of the familial risk is genetic in origin, with heritability estimates of approximately 60-80%. There have been fewer studies of BD-II, but its heritability has been found to be smaller (~46%) and closer to that of more common disorders such as major depressive disorder or generalized anxiety. Nevertheless, significant heritability does not necessarily imply the presence of genes of large effect, since the genetic risk for bipolar disorder appears likely to be spread across many common variants of small effect sizes. Ongoing studies of rare variations have found preliminary evidence for variants of slightly higher effect sizes, with initial evidence of convergence with common variations in genes associated with the synapse and the postsynaptic density.

While the likelihood that the testing of single variants or genes will be useful for diagnostic purposes is low, analyses known as polygenic risk studies can sum across all the risk loci and

have some ability to discriminate cases from controls, albeit at the group level rather than the individual level. These polygenic risk scores can also be used to identify shared genetic risk factors across other medical and psychiatric disorders. Bipolar disorder has strong evidence for common variant based coheritability with schizophrenia (genetic correlation (rg) 0.69) and major depressive disorder (rg 0.48). BD-I has stronger coheritability with schizophrenia compared with BD-II, which is more strongly genetically correlated with major depressive disorder (rg 0.66). Lower coheritability was observed with attention deficit hyperactivity disorder (rg 0.21), anorexia nervosa (0.20), and autism spectrum disorder (rg 0.21). These correlations provide evidence for shared genetic risk factors between bipolar disorder and other major psychiatric syndromes, a pattern also corroborated by recent nationwide registry based family studies.Nevertheless, despite their potential usefulness, polygenic risk scores must currently be interpreted with caution given their lack of populational representation and lingering concerns of residual confounds such as gene-environment correlations.

Insights from neuroimaging

Similarly to the early genetic studies, small initial studies had limited replication, leading to the formation of large worldwide consortiums such as ENIGMA (enhancing neuroimaging genetics through meta-analysis) which led to substantially larger sample sizes and improved reproducibility. In its volumetric analyses of subcortical structures from MRI (magnetic resonance imaging) of patients with bipolar disorder, the ENIGMA consortium found modest decreases in the volume of the thalamus (Cohen's d −0.15), the hippocampus (−0.23), and the amygdala (−0.11), with an increased volume seen only in the lateral ventricles (+0.26). Meta-analyses of cortical regions similarly found small reductions in cortical thickness broadly across the parietal, temporal, and frontal cortices (Cohen's d −0.11 to −0.29) but no changes in cortical surface area. In more recent meta-analyses of white matter tracts using diffuse tension imaging, widespread but modest decreases in white matter integrity were found throughout the brain in bipolar disorder, most notably in the corpus callosum and bilateral cinguli (Cohen's d −0.39 to −0.46). While these findings are likely to be highly replicable, they do not, as yet, have clinical application. This is because they reflect differences at a group level rather than an individual level, and because many of these patterns are also seen across other psychiatric disorders and could be either shared risk factors or the effects of confounding factors such as medical comorbidities, medications, co-occurring substance misuse, or the consequences (rather than causes) of living with mental illness. Efforts to collate and meta-analyze large samples utilizing longitudinal designs task based, resting state functional MRI measurents, as well as other measures of molecular imaging (magnetic resonance spectroscopy and positron emission tomography) are ongoing but not as yet synthesized in large scale meta-analyses.

Environmental risk factors

Because of the difficulty in measuring and studying the relevant and often common environmental risk factors for a complex illness like bipolar disorder, there has been less research on how environmental risk factors could cause or modify bipolar disorder. Evidence for intrauterine risk factors is mixed and less compelling than such evidence in disorders like schizophrenia. Preliminary evidence suggests that prominent seasonal changes in solar radiation, potentially through its effects on circadian rhythm, can be associated with an earlier onset of bipolar disorder and a higher likelihood of experiencing a depressive episode at onset. However, the major focus of environmental studies in bipolar disorder has been on traumatic and stressful life events in early childhood and in adulthood. The effects of such adverse events are complex, but on a broad level have been associated with earlier onset of bipolar disorder, a worse illness course, greater prevalence of psychotic symptoms, substance misuse and psychiatric comorbidities, and a higher risk of suicide attempts. Perhaps uniquely in bipolar disorder, evidence also indicates that positive life events associated with goal attainment can also increase the risk of developing elevated states.

Comorbidity

Bipolar disorder rarely manifests in isolation, with comorbidity rates indicating elevated lifetime risk of several co-occurring symptoms and comorbid disorders, particularly anxiety, attentional disorders, substance misuse disorders, and personality disorders. The causes of such comorbidity can be varied and complex: they could reflect a mixed presentation artifactually separated by current diagnostic criteria; they might also reflect independent illnesses; or they might represent the downstream effects of one disorder increasing the risk of developing another disorder. Anxiety disorders tend to occur before the frank onset of manic or hypomanic symptoms, suggesting that they could in part reflect prodromal symptoms that manifest early in the lifespan. Similarly, subthreshold and syndromic symptoms of attention deficit/hyperactivity disorder are also observed across the lifespan of people with bipolar disorder, but particularly in early onset bipolar disorder. On the other hand, alcohol and substance misuse disorders occur more evenly before and after the onset of bipolar disorder, consistent with a more bidirectional causal association.

The association between bipolar disorder and comorbid personality disorders is similarly complex. Milder manifestations of persistent mood instability (cyclothymia) or low mood (dysthymia) have previously been considered to be temperamental variants of bipolar disorder, but are now classified as related but separate disorders. In people with persistent emotional dysregulation, making the diagnosis of bipolar disorder can be particularly challenging, since the boundaries between longstanding mood instability and phasic changes in mood state can be difficult to distinguish. While symptom overlap can lead to artificially inflated prevalence rates of personality disorders in bipolar disorder, the elevated rates of most personality disorders in bipolar disorder, particularly those related to emotional instability, are likely reflective of an important clinical phenomenon that is understudied, particularly with regard to treatment implications. In general, people with comorbidities tend to have greater symptom burden and functional impairment and have lower response rates to treatment. Data on approaches to treat specific comorbid disorders in bipolar disorder are limited, and clinicians are often left to rely on their clinical judgment. The most parsimonious approach is to treat primary illness as fully as possible before considering additional treatment options for remaining comorbid symptoms. For certain comorbidities, such as anxiety symptoms and disorders of attention, first line pharmacological treatment—namely, antidepressants and stimulants, should be used with caution, since they might increase the long term risks of mood switching or overall mood instability.

Like other major mental illnesses, bipolar disorder is also associated with an increased prevalence of common medical disorders such as obesity, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, and thyroid dysfunction. These have been attributed to increase risk factors such as physical inactivity, poor nutrition, smoking, and increased use of addictive substances, but some could also be consequences of specific treatments, such as the atypical antipsychotics and mood stabilizers.Along with poor access to care, this medical burden likely accounts for much of the increased standardized mortality (approximately 2.6 times higher) in people with bipolar disorder, highlighting the need to utilize treatments with better long term side effect profiles, and the need for better integration with medical care.

Precursors and prodromes: who develops bipolar disorder?

While more widespread screening and better accessibility to mental health providers should in principle shorten the time to diagnosis and treatment, early manifestation of symptoms in those who ultimately go on to be diagnosed with bipolar disorder is generally non-specific. In particular, high risk offspring studies of adolescents with a parent with bipolar disorder have found symptoms of anxiety and attentional/disruptive disorders to be frequent in early adolescence, followed by higher rates of depression and sleep disturbance in later

teenage years. Subthreshold symptoms of mania, such as prolonged increases in energy, elated mood, racing thoughts, and mood lability are also more commonly found in children with prodromal symptoms (meta-analytic prevalence estimates ranging from 30-50%). Still, when considered individually, none of these symptoms or disorders are sensitive or specific enough to accurately identify individuals who will transition to bipolar disorder. Ongoing approaches to consider these clinical factors together to improve accuracy have a promising but modest ability to identify people who will develop bipolar disorder,emphasizing the need for further studies before implementation.

Screening for bipolar disorder

Manic episodes can vary from easily identifiable prototypical presentations to milder or less typical symptoms that can be challenging to diagnose. Ideally, a full diagnostic evaluation with access to close informants is performed on patients presenting to clinical care; however, evaluations can be hurried in routine clinical care, and the ability to recall previous episodes might be limited. In this context, the use of screening scales can be a helpful addition to clinical care, although screening scales must be regarded as an impetus for a confirmatory clinical interview rather than a diagnostic instrument by themselves. The two most widely used and openly available screening scales are the mood disorders questionnaire (based on the DSM-IV criteria for hypomania) and the hypomania check list (HCL-32),62 that represent a broader overview of symptoms proposed to be part of a broader bipolar spectrum.

Prognosis

Bipolar disorder is a recurrent illness, but its longitudinal course is heterogeneous and difficult to predict. The few available long term studies of BD-I and BD-II have found a consistent average rate of recurrence of 0.40 mood episodes per year in historical studies and 0.44 mood episodes per year in more recent studies. The median time to relapse is estimated to be 1.44 years, with higher relapse rates seen in BD-I (0.81 years) than in BD-II (1.63 years) and no differences observed with respect to age or sex. In addition to focusing on episodes, an important development in research and clinical care of bipolar disorder has been the recognition of the burden of subsyndromal symptoms. Although milder in severity, these symptoms can be long lasting, functionally impairing, and can themselves be a risk factor for episode relapse. Recent cohort studies have also found that a substantial proportion of patients with bipolar disorder (20-30%) continue to have poor outcomes even after receiving guideline based care. Risk factors that contribute to this poor outcome include transdiagnostic indicators of adversity such as substance misuse, low educational attainment, socioeconomic hardship, and comorbid disorders. As expected, those with more severe past illness activity, including those with rapid cycling, were also more likely to remain symptomatically and psychosocially impaired.

Treatment

The primary focus of treating bipolar disorder has been to manage the manic, mixed, or depressive episodes that present to clinical care and to subsequently prevent recurrence of future episodes. Owing to the relapse remitting nature of the illness, randomized controlled trials are essential to determine treatment efficacy, as the observation of clinical improvement could just represent the ebbs and flows of the natural history of the illness. In the United States, the FDA (Food and Drug Administration) requires at least two large scale placebo controlled trials (phase 3) to show significant evidence of efficacy before approving a treatment. Phase 3 studies of bipolar disorder are generally separated into short term studies of mania (3-4 weeks), short term studies for bipolar depression (4-6 weeks), and longer term maintenance studies to evaluate prophylactic activity against future mood episodes (usually lasting one year). Although the most rigorous evaluation of phase 3 studies would be to require two broadly representative and independent randomized controlled trials, the FDA permits consideration of so called enriched design trials that follow participants after an initial response and tolerability has been shown to an investigational drug. Because of this initial selection, such trials can be biased against comparator agents, and could be less

generalizable to patients seen in clinical practice.

A summary of the agents approved by the FDA for treatment of bipolar disorder is in table 1, which references the key clinical trials demonstrating efficacy. Figure 1 and supplementary table 1 are a comparison of treatments for mania, depression, and maintenance. Effect sizes reflect the odds ratios or relative risks of obtaining response (defined as ≥50% improvement from baseline) in cases versus controls and were extracted from meta-analyses of randomized controlled trials for bipolar depression and maintenance, as well as a network meta-analysis of randomized controlled trials in bipolar mania. Effect sizes are likely to be comparable for each phase of treatment, but not across the different phases, since methodological differences exist between the three meta-analytic studies.

Acute treatment of mania

As mania is characterized by impaired judgment, individuals can be at risk for engaging in high risk, potentially dangerous behaviors that can have substantial personal, occupational, and financial consequences. Therefore, treatment of mania is often considered a psychiatric emergency and is, when possible, best performed in the safety of an inpatient unit. While the primary treatment for mania is pharmacological, diminished insight can impede patients' willingness to accept treatment, emphasizing the significance of a balanced therapeutic approach that incorporates shared decision making frameworks as much as possible to promote treatment adherence.

The three main classes of anti-manic treatments are lithium, mood stabilizing anticonvulsants (divalproate and carbamazepine), and antipsychotic medications. Almost all antipsychotics are effective in treating mania, with the more potent dopamine D2 receptor antagonists such as risperidone and haloperidol demonstrating slightly higher efficacy (fig 1). In the United States, the FDA has approved the use of all second generation antipsychotics for treating mania except for lurasidone and brexpriprazole. Compared with mood stabilizing medications, second generation antipsychotics have a faster onset of action, making them a first line treatment for more severe manic symptoms that require rapid treatment.The choice of which specific second generation antipsychotic to use depends on a balance of efficacy, tolerability concerns, and cost considerations (see table 1). Notably, the FDA has placed a black box warning on all antipsychotics for increasing the risk of cerebral vascular accidents in the elderly. While this was primarily focused on the use of antipsychotics in dementia, this likely class effect should be taken into account when considering the use of antipsychotics in the elderly.

Traditional mood stabilizers, such as lithium, divalproate, and carbamazepine are also effective in the treatment of active mania (fig 1). Since lithium also has a robust prophylactic effect (see section on prevention of mood episodes below) it is often recommended as first line treatment and can be considered as monotherapy when rapid symptom reduction is not clinically indicated. On the other hand, other anticonvulsants such as lamotrigine, gabapentin, topiramate, and oxcarbazepine have not been found to be effective for the treatment of mania or mixed episodes. Although the empirical evidence for polypharmacy is limited, combination treatment in acute mania, usually consisting of a mood stabilizer and a second generation antipsychotic, is commonly used in clinical practice despite the higher burden of side effects. Following resolution of an acute mania, consideration should be given to transitioning to monotherapy with an agent with proven prophylactic activity.

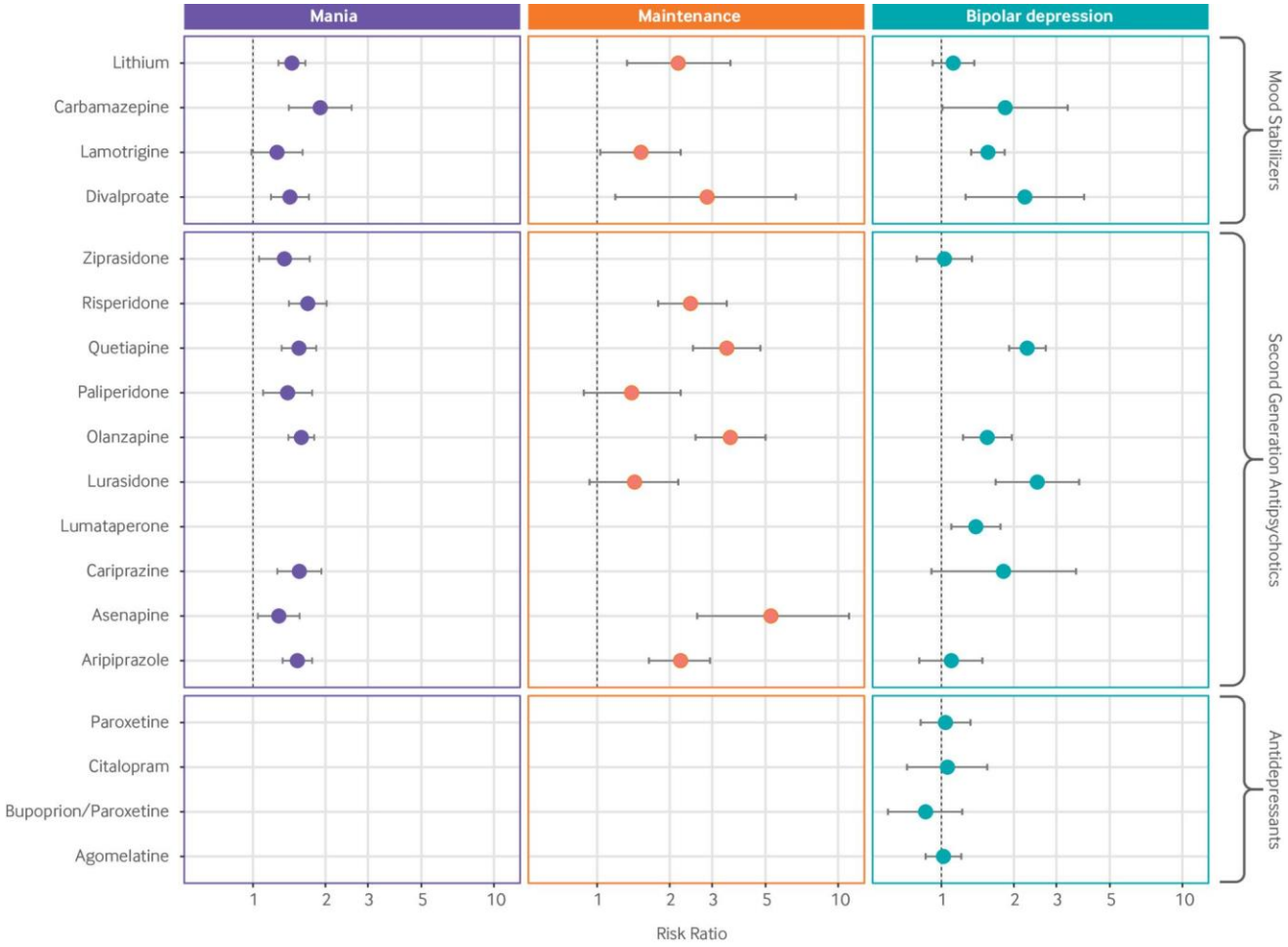
Table 1: FDA approved medications for bipolar disorder

Drug	Dosage	Notes	Main side effects
Treatment of mania and mixed episodes			
Lithium	Initial dose 300 mg twice a day Titrated to blood level of 0.8-1.2 mEq/L	• Approved 1970 • Most widely studied mood stabilizer • Blood levels essential for titration and maintenance	• Weight gain • Polyuria • Tremor • Hypothyroidism (~20%) • Hyperparathyroidism • Chronic kidney disease with long term use
Divalproex	Initial dose 750 mg a day Titrate to blood level of 50-120 mg/l	• Potentially most effective agent for mixed symptoms	• Somnolence • Weight gain • Alopecia • Mild thrombocytopenia • Elevation liver function tests • Hyperammonemia • Polycystic ovary syndrome (~20%) • Teratogenic (avoid in women of childbearing age)
Carbamazepine	Initial dose 200 mg twice a day Target dose 400-600 mg Titrate to blood levels between 4-12 mg/l	• Potent CYP3A4 autoinducer with frequent drug interactions	• Dizziness, ataxia • Syndrome of inappropriate antidiuretic hormone secretion (<5%) • Transient hematological abnormalities • Severe rash/Stevens-Johnson syndrome (~0.01%; higher risk in people of Asian descent) • Teratogenic (avoid in women of childbearing age)
Chlorpromazine	Initial dose 10-25 mg three times a day Target dose 200-600 mg	• Approved 1973 • Only typical antipsychotic approved for mania • Rarely used in current practice	• Extrapyramidal symptoms • Sedation • Weight gain • Non-specific electrocardiogram changes • Increased risk cerebrovascular accidents in elderly
Risperidone	Target dose 1-6 mg a day	• Available in a 2 week long acting formulation	• Extrapyramidal symptoms • Weight gain

Drug	Dosage	Notes	Main side effects
			• Hyperprolactinemia • Orthostatic hypotension
Olanzapine	10-20 mg	• Available in a monthly long acting formulation	• Sedation • Prominent weight gain • Hyperglycemia • Metabolic syndrome
Quetiapine	Initial dose 50 mg at night Target dose 400-800 mg at night	• Few extrapyramidal symptoms	• Somnolence • Dizziness • Weight gain • Hyperglycemia • Metabolic syndrome
Ziprasidone	Initial dose 20 mg twice a day Max 80 mg twice a day	• Weight neutral • Approved only as adjunct to lithium or divalproate	• QT interval prolongation • Mild akathisia
Aripiprazole	Initial dose 5-10 mg a day Up to 30 mg max	• Weight neutral • Available in long acting formulation	• Akathisia • Anxiety
Asenapine	Initial dose 5 mg twice a day Max 10 mg twice a day		• Sedation • Mild weight gain

Drug	Dosage	Notes	Main side effects
Treatment of bipolar depression			
Olanzapine-fluoxetine	Initial dose 6-25 mg a day Max dose 12-50 mg a day	• Rarely used because of side effect burden	• Weight gain • Metabolic syndrome
Quetiapine	Initial dose 50 mg at night Target dose 300 mg at night	• FDA approved for all phases of bipolar disorder illness • Approved for depressive episodes associated with BD-I and BD-II	• Somnolence • Dizziness • Weight gain • Metabolic syndrome • Rare (cataracts)
Lurasidone	Initial dose 20 mg a day (with food) Max 80 mg once a day	• Weight neutral	• Mild sedation • Akathisia
Cariprazine	Initial dose 1.5 mg a day Target dose 1.5 mg to 3 mg a day	• Weight neutral	• Extrapyramidal symptoms • Akathisia
Lumateperone	Target dose 42 mg a day	• Approved for depressive episodes associated with BD-I and BD-II • Single dose, no titration required	• Mild sedation, somnolence

Drug	Dosage	Notes	Main side effects
Treatment for bipolar disorder prevention (maintenance)			
Lithium	Initial dose 300 mg twice a day Titrated to blood level of 0.6-0.8 mEq/L	• Approved 1970 • Most widely studied mood stabilizer • Blood levels essential for titration and maintenance	• Common: weight gain • Mild tremor • Hypothyroidism • Hypoparathyroidism • Diabetes insipidus • Chronic renal insufficiency
Lamotrigine	Initial dose 25 mg once a day Titration schedule up to 200 mg once a day	• Well tolerated • Weight neutral • Slow titration limits treatment of acute depression	• Rash (5-10%) • Severe rash/Stevens-Johnson syndrome (0.1-0.01%) • Slower titration schedule and dose if administered with divalproate, an inhibitor of CYP3A • Might require higher doses when administered with carbamazepine, an activator of CYP3A activator
Quetiapine	Initial dose 50 mg at night Target dose 400-800 mg at night	• Approved only as adjunct to lithium or divalproate	• Somnolence • Dizziness • Weight gain • Metabolic syndrome • Rare (cataracts)
Ziprasidone	Initial dose 20 mg twice a day Max 80 mg twice a day	• Well tolerated • Weight neutral • Approved only as adjunct to lithium or divalproate	• QT interval prolongation
Aripiprazole	15-30 mg a day	• As monotherapy or adjunct to lithium or divalproate • Efficacy appears primarily in prevention of manic relapse • Available in a monthly long acting injection	• Akathisia • Extrapyramidal symptoms
Asenapine	Initial dose 5 mg twice a day Max 10 mg twice a day	• Sublingual administration	• Sedation • Weight gain



Summary of treatment response rates (defined as ≥50% improvement from baseline) of modern clinical trials for acute mania, acute bipolar depression, and long term recurrence. Meta-analytic estimates were extracted from recent meta-analyses or network meta-analyses of acute mania,acute bipolar depression, and bipolar maintenance studies

Pharmacological approaches to bipolar depression

Depressed episodes are usually more common than mania or hypomania, and often represent the primary reason for individuals with bipolar disorder to seek treatment. Nevertheless, because early antidepressant randomized controlled trials did not distinguish between unipolar and bipolar depressive episodes, it has only been in the past two decades that large scale randomized controlled trials have been conducted specifically for bipolar depression. As such trials are almost exclusively funded by pharmaceutical companies, they have focused on the second generation antipsychotics and newer anticonvulsants still under patent. These trials have shown moderate but robust effects for most recent second generation antipsychotics, five of which have received FDA approval for treating bipolar depression (table 1). No head-to-head trials have been conducted among these agents, so the choice of medication depends on expected side effects and cost considerations. For example, quetiapine has robust antidepressant efficacy data but is associated with sedation, weight gain, and adverse cardiovascular outcomes. Other recently approved medications such as lurasidone, cariprazine, and lumateperone have better side effect profiles but show more modest antidepressant activity.

Among the mood stabilizing anticonvulsants, lamotrigine has limited evidence for acute antidepressant activity, possibly owing to the need for an 8 week titration to reach the full dose of 200 mg. However, as discussed below, lamotrigine can still be considered for mild to moderate acute symptoms owing to its generally tolerable side effect profile and proven effectiveness in preventing the recurrence of depressive episodes. Divalproate and carbamazepine have some evidence of being effective antidepressants in small studies, but as there has been no large scale confirmatory study, they should be considered second or third line options.Lithium has been studied for the treatment of bipolar depression as a comparator to quetiapine and was not found to have a significant acute antidepressant effect.

Antidepressants

Owing to the limited options of FDA approved medications for bipolar depression and concerns of metabolic side effects from long term second generation antipsychotic use, clinicians often resort to the use of traditional antidepressants for the treatment of bipolar depression despite the lack of FDA approval for such agents. Indeed, recent randomized clinical trials of antidepressants in bipolar depression have not shown an effect for paroxetine, bupropion,or agomelatine. Beyond the question of efficacy, another concern regarding antidepressants in bipolar disorder is their potential to worsen the course of illness by either promoting mixed or manic symptoms or inducing more subtle degrees of mood instability and cycle acceleration. However, the risk of switching to full mania while being treated with mood stabilizers appears to be modest, with a meta-analysis of randomized clinical trials and clinical cohort studies showing the rates of mood switching over an average follow-up of five months to be approximately 15.3% in people with bipolar disorder treated on antidepressants compared with 13.8% in those without antidepressant treatment. The risk of switching appears to be higher in the first 1-2 years of treatment in people with BD-I, and in those treated with a tricyclic antidepressant or the dual reuptake inhibitor venlafaxine. Overall, while the available data have methodological limitations, most guidelines do not recommend the use of antidepressants in bipolar disorder, or recommend them only after agents with more robust evidence have been tried. That they remain so widely used despite the equivocal evidence base reflects the unmet need for treatment of depression, concerns about the long term side effects of second generation antipsychotics, and the challenges of changing longstanding prescribing patterns.

Pharmacological approaches to prevention of recurrent episodes

Following treatment of the acute depressive or manic syndrome, the major focus of treatment is to prevent future episodes and minimize interepisodic subsyndromal symptoms. Most often, the medication that has been helpful in controlling the acute episode can be continued for prevention, particularly if clinical trial evidence exists for a maintenance effect. To show efficacy for prevention, studies must be

sufficiently long to allow the accumulation of future episodes to occur and be potentially prevented by a therapeutic intervention. However, few long term treatment studies exist and most have utilized enriched designs that likely favor the drug seeking regulatory approval. As shown in figure 1, meta-analyses show prophylactic effect for most (olanzapine, risperidone, quetiapine, aripiprazole, asenapine) but not all (lurasidone, paliperidone) recently approved second generation antipsychotics. The effect sizes are generally comparable with monotherapy (odds ratio 0.42, 95% confidence interval 0.34 to 0.5) or as adjunctive therapy (odds ratio 0.37, 95% confidence interval 0.25 to 0.55). Recent studies of lithium, which have generally used it as a (non-enriched) comparator drug, show a comparable protective effect (odds ratio 0.46, 95% confidence interval 0.28 to 0.75). Among the mood stabilizing anticonvulsant drugs, a prophylactic effect has also been found for both divalproate and lamotrigine (fig 1 and supplementary table 1), although only the latter has been granted regulatory approval for maintenance treatment. While there are subtle differences in effect sizes in drugs approved for maintenance (fig 1 and table 1), the overlapping confidence intervals and methodological differences between studies prevent a strict comparison of the effect measures.

Guidelines often recommend lithium as a first line agent given its consistent evidence of prophylaxis, even when tested as the disadvantaged comparator drug in enriched drug designs. Like other medications, lithium has a unique set of side effects and ultimately the decision about which drug to use among those which are efficacious should be a decision carefully weighed and shared between patient and provider. The decision might be re-evaluated after substantial experience with the medication or at different stages in the long term treatment of bipolar disorder (see table 1).

Psychotherapeutic approaches

The frequent presence of residual symptoms, often associated with psychosocial and occupational dysfunction, has led to renewed interest in psychotherapeutic and psychosocial approaches to bipolar disorder. Given the impairment of judgment seen in mania, psychotherapy has more of a supportive and educational role in the treatment of mania, whereas it can be more of a primary focus in the treatment of depressive states. On a broad level, psychotherapeutic approaches effective for acute depression, such as cognitive behavioral therapy, interpersonal therapy, behavioral activation, and mindfulness based strategies, can also be recommended for acute depressive states in individuals with bipolar disorder. Evidence for more targeted psychotherapy trials for bipolar disorder is more limited, but meta-analyses have found evidence for decreased recurrence (odds ratio 0.56; 95% confidence interval 0.43 to 0.74) and improvement of subthreshold interepisodic depressive and manic symptoms with cognitive behavioral therapy, family based therapy, interpersonal and social rhythm therapy, and psychoeducation. Recent investigations have also focused on targeted forms of psychotherapy to improve cognitio as well as psychosocial and occupational functioning. Although these studies show evidence of a moderate effect, they remain preliminary, methodologically diverse, and require replication on a larger scale.

The implementation of evidence based psychotherapy as a treatment faces several challenges, including clinical training, fidelity monitoring, and adequate reimbursement. Novel approaches, leveraging the greater tractability of digital tools and allied healthcare workers, are promising means of lessening the implementation gap; however, these approaches require validation and evidence of clinial utility similar to traditional methods.

Neurostimulation approaches

For individuals with bipolar disorder who cannot tolerate or do not respond well to standard pharmacotherapy or psychotherapeutic approaches, neurostimulation techniques such as repetitive transcranial magnetic stimulation or electric convulsive therapy should be considered as second or third line treatments. Electric convulsive therapy has shown response rates of approximately 60-80% in severe acute depressions and 50-60% in cases with treatment

resistant depression. These response rates compare favorably with those of pharmacological treatment, which are likely to be closer to ~50% and ~30% in subjects with moderate to severe depression and treatment resistant depression, respectively. Although the safety of electric convulsive therapy is well established, relatively few medical centers have it available, and its acceptability is limited by cognitive side effects, which are usually short term, but which can be more significant with longer courses and with bilateral electrode placement. While there have been fewer studies of electric convulsive therapy for bipolar depression compared with major depressive disorder, it appears to be similarly effective and might show earlier response. Anecdotal evidence also suggests electric convulsive therapy that is useful in refractory mania.

Compared with electric convulsive therapy, repetitive transcranial magnetic stimulation has no cognitive side effects and is generally well tolerated. Repetitive transcranial magnetic stimulation acts by generating a magnetic field to depolarize local neural tissue and induce excitatory or inhibitory effects depending on the frequency of stimulation. The most studied FDA approved form of repetitive transcranial magnetic stimulation applies high frequency (10 Hz) excitatory pulses to the left prefrontal cortex for 30-40 minutes a day for six weeks. Like electric convulsive therapy, repetitive transcranial magnetic stimulation has been primarily studied in treatment resistant depression and has been found to have moderate effect, with about one third of patients having a significant treatment response compared with those treated with pharmacotherapy. Recent innovations in transcranial magnetic stimulation have included the use of a novel, larger coil to stimulate a larger degree of the prefrontal cortex (deep transcranial magnetic stimulation), and a shortened (three minutes), higher frequency intermittent means of stimulation known as theta burst stimulation that appears to be comparable to conventional (10 Hz) repetitive transcranial magnetic stimulation. A preliminary trial has recently assessed a new accelerated protocol of theta burst stimulation marked by 10 sessions a day for five days. It found that theta burst stimulation had a greater effect on people with treatment resistant depression compared with treatment as usual, although larger studies are needed to confirm these findings.

Conventional repetitive transcranial magnetic stimulation (10 Hz) studies in bipolar disorder have been limited by small sample sizes but have generally shown similar effects compared with major depressive disorder. However, a proof of concept study of single session theta burst stimulation did not show efficacy in bipolar depression, reiterating the need for specific trials for bipolar depression. Given the lack of such trials in bipolar disorder, repetitive transcranial magnetic stimulation should be considered a potentially promising but as yet unproven treatment for bipolar depression.

The other major form of neurostimulation studied in both unipolar and bipolar depression is transcranial direct current stimulation, an easily implemented method of delivering a low amplitude electrical current to the prefrontal area of the brain that could lead to local changes in neuronal excitability. Like repetitive transcranial magnetic stimulation, transcranial direct current stimulation is well tolerated and has been mostly studied in unipolar depression, but has not yet generated sufficient evidence to be approved by a regulatory agency. Small studies have been performed in bipolar depression, but the results have been mixed and require further research before use in clinical settings. Finally, the evidence for more invasive neurostimulation studies such as vagal nerve stimulation and deep brain stimulation remains extremely limited and is currently insufficient for clinical use.

Treatment resistance in bipolar disorder

As in major depressive disorder, the use of term treatment resistance in bipolar disorder is controversial since differentiating whether persistent symptoms are caused by low treatment adherence, poor tolerability, the presence of comorbid disorders, or are the result of true treatment resistance, is an essential but often challenging clinical task. Treatment resistance should only be considered

after two or three trials of evidence based monotherapy, adjunctive therapy, or both. In difficult-to-treat mania, two or more medications from different mechanistic classes are typically used, with electric convulsive therapy and clozapine being considered if more conventional anti-manic treatments fail. In bipolar depression, it is common to combine antidepressants with anti-manic agents, despite limited evidence for efficacy.Adjunctive therapies such as bright light therapy, the dopamine D2/3 receptor agonist pramipexole, and ketamine have shown promising results in small open label trials that require further study.

Treatment considerations to reduce suicide in bipolar disorder

The risk of completed suicide is high across the subtypes of bipolar disorder, with estimated rates of 10-15% across the lifespan. Lifetime rates of suicide attempts are much higher, with almost half of all individuals with bipolar disorder reporting at least one attempt. Across a population and, often within individuals, the causes of suicide attempts and completed suicides are likely to be multifactorial, affected by various risk factors, such as symptomatic illness, environmental stressors, comorbidities (particularly substance misuse), trait impulsivity, interpersonal conflict, loneliness, or socioeconomic distress.Risk is highest in depressive and dysphoric/mixed episodes and is particularly high in the transitional period following an acute admission to hospital.Among the available treatments, lithium has potential antisuicidal properties. However, since suicide is a rare event, with very few to zero suicides within a typical clinical trial, moderate evidence for this effect emerges only in the setting of meta-analyses of clinical trials. Several observational studies have shown lower mortality in patients on lithium treatment but such associations might not be causal, since lithium is potentially fatal in overdose and is often avoided by clinicians in patients at high risk of suicide.

The challenge of studying scarce events has led most studies to focus on the reduction of the more common phenomena of suicidal ideation and behavior as a proxy for actual suicides. A recent such multisite study of the Veterans Affairs medical system included a mixture of unipolar and bipolar disorder and was stopped prematurely for futility, indicating no overall effect of moderate dose lithium. Appropriate limitations of this study have been noted, including difficulties in recruitment, few patients with bipolar disorder (rather than major depressive disorder), low levels of compliance with lithium therapy, high rates of comorbidity, and a follow-up of only one year. Nevertheless, while the body of evidence suggests that lithium has a modest antisuicidal effect, its degree of protection and utility in complex patients with comorbidities and multiple risk factors remain matters for further study. Treatment of specific suicidal risk in patients with bipolar disorder must therefore also incorporate broader interventions based on the individual's specific risk factors. Such an approach would include societal interventions like means restriction and a number of empirically tested suicide focused psychotherapy treatments.Unfortunately, the availability of appropriate training, expertise, and care models for such treatments remains limited, even in higher income countries.

Treatment consideration in BD-II and bipolar spectrum conditions

Because people with BD-II primarily experience depressive symptoms and appear less likely to switch mood states compared with individuals with BD-I,50171 there has been a greater acceptance of the use of antidepressants in BD-II depression, including as monotherapy. However, caution should be exercised when considering the use of antidepressants without a mood stabilizer in patients with BD-II who might also experience high rates of mood instability and rapid cycling. Such individuals can instead respond better to newer second generation antipsychotic agents such as quetiapine and lumateperone, which are supported by post hoc analyses of these more recent clinical trials with more BD-II patients. In addition, despite the absence of randomized controlled trials, open label studies have suggested that lithium and other mood stabilizers can have similar efficacy in BD-II, especially in the case of lamotrigine.

Psychotherapeutic approaches such as psychoeducation, cognitive behavioral therapy, and interpersonal and social rhythm therapy have been found to be helpful and can be considered as the primary form of treatment for BD-II in some patients, although in most clinical scenarios BD-II is likely to occur in conjunction with psychopharmacology. While it can be tempting to consider BD-II a milder variant of BD-I, high rates of comorbid disorders, rapid cycling, and adverse consequences such as suicide attempts highlight the need for clinical caution and the provision of multimodal treatment, focusing on mood improvement, emotional regulation, and better psychosocial functioning.

Precision medicine: can it be applied to improve the care of bipolar disorder?

The recent focus on precision medicine approaches to psychiatric disorders seeks to identify clinically relevant heterogeneity and identify characteristics at the level of the individual or subgroup that can be leveraged to identify and target more efficacious treatments.

The utility of such an approach was originally shown in oncology, where a subset of tumors had gene expression or DNA mutation signatures that could predict response to treatments specifically designed to target the aberrant molecular pathway. While much of the emphasis of precision medicine has been on the eventual identification of biomarkers utilizing high throughput approaches (genetics and other "omics" based measurements), the concept of precision medicine is arguably much broader, encompassing improvements in measurement, potentially through the deployment of digital tools, as well as better conceptualization of contextual, cultural, and socioeconomic mechanisms associated with psychopathology. Ultimately, the goal of precision psychiatry is to identify and target driving mechanisms, be they molecular, physiological, or psychosocial in nature. As such, precision psychiatry seeks what researchers and clinicians have often sought: to identify clinically relevant heterogeneity to improve prediction of outcomes and increase the likelihood of therapeutic success. The novelty being not so much the goals of the overarching approach, but the increasing availability of large samples, novel digital tools, analytical advances, and an increasing armamentarium of biological measurements that can be deployed at scale.

Although not unique to bipolar disorder, several clinical decision points along the life course of bipolar disorder would benefit from a precision medicine approach. For example, making an early diagnosis is often not possible based on clinical symptoms alone, since such symptoms are usually non-specific. A precision medicine approach could also be particularly relevant in helping to identify subsets of patients for whom the use of antidepressants could be beneficial or harmful. Admittedly, precision medicine approaches to bipolar disorder are still in their infancy, and larger, clinically relevant, longitudinal, and reliable phenotypes are needed to provide the infrastructure for precision medicine approaches. Such data remain challenging to obtain at scale, leading to renewed efforts to utilize the extant clinical infrastructure and electronic medical records to help emulate traditional longitudinal analyses. Electronic medical records can help provide such data, but challenges such as missingness, limited quality control, and potential biases in care need to be resolved with carefully considered analytical designs.

Emerging treatments

Two novel atypical antipsychotics, amilsupride and bifeprunox, are currently being tested in phase 3 trials (NCT05169710 and NCT00134459) and could gain approval for bipolar depression in the near future if these pivotal trials show a significant antidepressant effect. These drugs could offer advantages such as greater antidepressant effects, fewer side effects, and better long term tolerability, but these assumptions must be tested empirically. Other near term possibilities include novel rapid antidepressant treatments, such as (es)ketamine that putatively targets the glutamatergic system, and has been recently approved for treatment resistant depression, but which have not yet been tested in phase 3 studies in bipolar depression. Small studies have shown comparable effects of intravenous ketamine, in

bipolar depression with no short term evidence of increased mood switching or mood instability. Larger phase 2 studies (NCT05004896) are being conducted which will need to be followed by larger phase 3 studies. Other therapies targeting the glutamatergic system have generally failed phase 3 trials in treatment resistant depression, making them unlikely to be tested in bipolar depression. One exception could be the combination of dextromethorphan and its pharmacokinetic (CYP2D6) inhibitor bupropion, which was recently approved for treatment resistant depression but has yet to be tested in bipolar depression. Similarly, the novel GABAergic compound zuranolone is currently being evaluated by the FDA for the treatment of major depressive disorder and could also be subsequently studied in bipolar depression.

Unfortunately, given the general efficacy for most patients of available treatments, few scientific and financial incentives exist to perform large scale studies of novel treatment in mania. Encouraging results have been seen in small studies of mania with the selective estrogen receptor modulator tamoxifen and its active metabolite endoxifen, both of which are hypothesized to inhibit protein kinase C, a potential mechanistic target of lithium treatment. These studies remain small, however, and anti-estrogenic side effects have potentially dulled interest in performing larger studies.

Finally, several compounds targeting alternative pathophysiological mechanisms implicated in bipolar disorder have been trialed in phase 2 academic studies. The most studied has been N-acetylcysteine, a putative mitochondrial modulator, which initially showed promising results only to be followed by null findings in larger more recent studies. Similarly, although small initial studies of anti-inflammatory agents provided impetus for further study, subsequent phase 2 studies of the non-steroidal agent celecoxib, the anti-inflammatory antibiotic minocycline, and the antibody infliximab (a tumor necrosis factor antagonist) have not shown efficacy for bipolar depression. Secondary analyses have suggested that specific anti-inflammatory agents might be effective only for a subset of patients, such as those with elevated markers of inflammation or a history of childhood adversity; however, such hypotheses must be confirmed in adequately powered independent studies.

Guidelines

Several international guidelines for the treatment of bipolar disorder have been published in the past decade, providing a list of recommended treatments with efficacy in at least one large randomized controlled trial. Since effect sizes tend to be moderate and broadly comparable across classes, all guidelines allow for significant choice among first line agents, acknowledging that clinical characteristics, such as history of response or tolerability, severity of symptoms, presence of mixed features, or rapid cycling can sometimes over-ride guideline recommendations. For acute mania requiring rapid treatment, all guidelines prioritize the use of second generation antipsychotics such as aripiprazole, quetiapine, risperidone, asenapine, and cariprazine.Combination treatment is considered based on symptom severity, tolerability, and patient choice, with most guidelines recommending lithium or divalproate along with a second generation antipsychotic for mania with psychosis, severe agitation, or prominent mixed symptoms. While effective, haloperidol is usually considered a second choice option owing to its propensity to cause extrapyramidal symptoms. Uniformly, all guidelines agree on the need to taper antidepressants in manic or mixed episodes.

For maintenance treatment, guidelines are generally consistent in recommending lithium if tolerated and without relative contraindications, such as baseline renal disease. The second most recommended maintenance treatment is quetiapine, followed by aripiprazole for patients with prominent manic episodes and lamotrigine for patients with predominant depressive episodes. Most guidelines recommend considering prophylactic properties when initially choosing treatment for acute manic episodes, although others suggests that acute maintenance treatments can be cross tapered

with maintenance medications after several months of full reponse.

For bipolar depression, recent guidelines recommend specific second generation antipsychotics such as quetiapine, lurasidone, and cariprazine. For more moderate symptoms, consideration is given to first using lamotrigine and lithium. Guidelines remain cautious about the use of antidepressants (selective serotonin reuptake inhibitors, venlafaxine, or bupropion) in patients with BP-I, restricting them to second or third line treatments and always in the context of an anti-manic agent. However, for patients with BP-II and no rapid cycling, several guidelines allow for the use of carefully monitored antidepressant monotherapy.

Conclusion

Bipolar disorder is a highly recognizable syndrome with many effective treatment options, including the longstanding gold standard therapy lithium. However, a significant proportion of patients do not respond well to current treatments, leading to negative consequences, poor quality of life, and potentially shortened lifespan. Several novel treatments are being developed but limited knowledge of the biology of bipolar disorder remains a major challenge for novel drug discovery. Hope remains that the insights of genetics, neuroimaging, and other investigative modalities could soon be able to inform the development of rational treatments aimed to mitigate the underlying pathophysiology associated with bipolar disorder. At the same time, however, efforts are needed to bridge the implementation gap and provide truly innovative and integrative care for patients with bipolar disorder. Owing to the complexity of bipolar disorder, few patients can be said to be receiving optimized care across the various domains of mental health that are affected in those with bipolar disorder. Fortunately, the need for improvement is now well documented, and concerted efforts at the scale necessary to be truly innovative and integrative are now on the horizon.

https://www.bmj.com/content/381/bmj-2022-073591

Met dank aan dr. Lesly Vander Ginst

HET CANNABINOÏD-HYPEREMESISSYNDROOM: WEINIG BEKEND ?

Waarschijnlijk komt het relatief onbekende cannabinoïd-hyperemesissyndroom vaker voor dan we denken, dus vandaar is het belangrijk om een goede anamnese naar middelengebruik en douche- en badgewoontes af te nemen.

Casus: een dame, 28 jaar oud, moet sinds 2 dagen excessief braken en heeft forse maagpijn:

Anamnese:

- Het euvel is begonnen op een feestje waar ze meerdere glazen alcohol genuttigd heeft.
- Ze heeft geen koorts en haar stoelgang is normaal en enkel heet douchen helpt tegen de klachten.
- Ze is bang dat ze gedrogeerd is.
- Bij navraag rookt ze al een aantal jaren 3 keer wiet per week.

- Differentiaaldiagnose: haar huisarts denkt aan een alcohol- of drugsintoxicatie, pancreatitis en hyperemesis gravidarum.

Enkele cijfers:

- 23,7% van de Nederlandse bevolking van 18 jaar en ouder, zo'n 3,2 miljoen mensen, heeft in 2018 ooit cannabis gebruikt:
  - Het percentage van gebruik tijdens de afgelopen maand ligt een stuk lager, 4,6% of zo'n 620.000 mensen.
  - 200.000 mensen (1,6%) blijven(bijna) dagelijks blowen.
- Voornaamste bestanddelen van cannabis zijn delta-9-tetrahydrocannabinol (THC) en cannabidiol (CBD).
- Omdat het grotendeels accumuleert in vetweefsel heeft THC een lange halfwaardetijd: deze ligt tussen de 24,9 en 35,3 uur.
- THC heeft o.a. een anti-emetisch effect op het centraal zenuwstelsel:
  - Er lijkt echter een tegengesteld effect op te treden bij chronisch gebruik.
  - Dit heeft een vertraagde maaglediging tot gevolg met daarbij misselijkheid en braken.

Cannabis als medicijn:

- Bij meerdere uiteenlopende aandoeningen wordt cannabis ingezet:
  - Gebeurt bvb. om misselijkheid en braken door chemotherapie tegen te gaan.
  - Het stimuleren van de eetlust bij hiv/aids en het bestrijden van chronische pijn.
  - Wordt gebruikt bij multipele sclerose en ook bij depressie.
- Het voorschrijven van cannabis wordt door het NHG niet aanbevolen:
  - Er is immers onvoldoende wetenschappelijk bewijs voor pijnreductie of verbetering van de kwaliteit van leven.
  - Er kunnen echter wel bijwerkingen optreden.
- Advies van het NHG is om het gebruik enkel te overwegen in de palliatieve fase bij patiënten met (pijn)klachten bij wie de gangbare behandeling onvoldoende helpt of te veel bijwerkingen oplevert.

Casus: verdere aanpak:

- De huisarts zendt patiënte onder de waarschijnlijkheidsdiagnose cannabinoid-hyperemesissyndroom naar het ziekenhuis omdat ze waarschijnlijk uitgedroogd is:
  - Ze krijgt daar een symptomatische behandeling met anti-emetica en intraveneus vocht.
  - Ze stopt met cannabis waarna de klachten binnen 2 dagen verdwenen zijn.
- Ze verliest vanaf het begin van de symptomen in totaal bijna 10 kg aan gewicht en is enkele weken na de opname volledig hersteld.

Epidemiologie en symptomen:

- Het syndroom is beschreven in case reports en case series en daardoor beschikt men niet over goede epidemiologische gegevens.
- Verder is er niets bekend over hoe vaak het syndroom voorkomt in vergelijking met andere bijwerkingen van cannabis.
- Het syndroom vertoont wel een grote overlap met het cyclisch braken syndroom:
  - Het kenmerkt zich volgens de Rome IV-criteria door stereotypisch episodisch braken dat minder dan 1 week duurt
  - In de afgelopen 3 maanden zijn er daarbij symptomen aanwezig en zijn er minimaal3 episodes in het afgelopen jaar en 2 episodes in de afgelopen 6 maanden.
  - Er is minimaal 1 week tussen de episodes waarin de patiënt niet braakt.
- De symptomen treden op na chronisch gebruik van cannabis en verlichting van cyclisch braken treedt op na lange abstinentie van cannabisgebruik.
- De Rome IV-criteria doen geen uitspraak over de duur en frequentie van het chronisch gebruik van cannabis en de abstinentie.
- Aan de Rome IV-criteria is het dwangmatig nemen van baden of douches met heet water als ondersteunend kenmerk toegevoegd.
- Dit aangeleerd gedrag gaat misselijkheid en braken tegen, en dat wordt vaak per toeval ontdekt.

Vaak doorloopt een patiënt 3 fasen:

- Een **prodromale** fase:
  - Kan maanden tot jaren duren.
  - Gaat gepaard met misselijkheid zonder braken, anorexie, abdominaal discomfort en angst voor braken.
- Een **hyperemesis** fase:
  - Duurt dagen tot weken.
  - Hier ziet men een cyclisch patroon van misselijkheid en braken, waarbij heet douchen of baden vaak kortdurende verlichting kan geven.
  - Vaak gaat deze fase gepaard met sympathische overactiviteit (tremor, tachycardie, hypertensie, zweten en opvliegers).
  - Men ziet ook vaak diffuse maar relatief milde buikpijn.
  - De patiënt kan tijdens deze periode wel 5-10 kg afvallen, met soms uitdroging en elektrolytenstoornissen, waarvoor ziekenhuisopname nodig is.
- Een **herstel**fase:
  - Hierbij zijn er dagen tot maanden geen klachten meer.
  - Het gewicht kan herstellen en de patiënt eet weer normaal.

Pathofysiologie:

- Er is weinig over bekend, vooral omdat er weinig onderzoek naar verricht is, maar er zijn wel verschillende hypotheses over mogelijke oorzaken.
- Eerste hypothese:
  - Het endocannabinoïd-systeem zou een rol spelen bij gastro-intestinale mobiliteit, misselijkheid/braken, stemming, slaap en pijn.
  - Het systeem omvat een groep van cannabinoïd-receptoren (CB-1 en CB-2) die in o.a. de hersenen en het gastro-intestinaal stelsel te vinden zijn.
  - Er bestaat beperkt bewijs dat suggereert dat de complexe farmacodynamiek bij de CB-1-receptor een rol speelt.
  - Mogelijke mechanismen hiervan zijn o.a. de dichtheid van de receptoren, interactie met actieve cannabismetabolieten en potentie van bestandsdelen van cannabis.
- Andere hypothese:
  - Er is mogelijk sprake van een genetische variatie in het enzymmetabolisme van THC, naast een variatie in de cannabinoïd-componenten van individuele planten.
  - Deze genetische variatie kan verklaren waarom lang niet alle mensen die cannabis gebruiken last krijgen van hyperemesis.

Behandeling:

- Deze richt zich op het verminderen van de symptomen tijdens de hyperemesisfase en het voorkomen van recidieven:
- Symptomatische behandeling:
  - Heet douchen of baden, maar het mechanisme hierachter is onbekend.

- Dit gedrag verdwijnt na de hyperemesisfase.
- Men kan anti-emetica proberen, maar deze hebben vaak maar een minimaal of geen effect op de klachten.

- Voor het effect van topicale capsaïcinecrème bestaat er beperkt bewijs:
  - Activatie van de TRPV-1-receptor interfereert hierbij mogelijk met het endocanabinoïd-systeem.
  - Deze receptoren bevinden zich o.a. in de tractus digestivus en bij het medullaire braakcentrum (chemoreceptoren in de medulla oblongata), vaak in de nabijheid van eenCB-1-receptor.
- Dit zou er kunnen op wijzen dat er op beide locaties een interactie plaatsvindt:
  - De door warmte geactiveerde TRPV-1 – receptor remt substance P, een neuropeptide die een rol speelt bij misselijkheid en braken.
  - Warmte activeert TRPV-1-receptoren (>43 °C), en dat verklaart mogelijk waarom heet douchen of baden de klachten verlicht.

- Soms is er ondersteunende therapie nodig bij dreigende dehydratie in de vorm van intraveneuze rehydratie.
- Men kan recidieven enkel voorkomen door het cannabisgebruik volledig te staken.
- De klachten kunnen na het staken van het cannabisgebruik nog dagen tot weken aanhouden door de lange halfwaardetijd van THC en omdat het vetoplosbaar is.

Besluit:

- Misselijkheid, buikklachten, recidiverend braken, allemaal symptomen die passen in een brede differentiaaldiagnose:
  - Bij anamnese moeten we hier actief vragen naar middelengebruik en bad- en /of douchegewoonten.
  - Omdat ze niet op de hoogte zijn van het bestaan ervan, missen huisartsen waarschijnlijk vaak het cannabinoïd-hyperemesissyndroom.
- Drie bevindingen zouden ons op het spoor moeten zetten van het syndroom: het chronisch gebruik van cannabis (> 1 jaar), het cyclisch optreden van ernstige misselijkheid en braken en het dwangmatig nemen van hete baden of douches.

- Helaas is de pathofysiologie hierachter nog onvoldoende opgehelderd.
- Nadat de patiënt met cannabisgebruik gestopt is, verdwijnen de symptomen volledig.

Huisarts & Wetenschap december 2023 pag. 32-34.

Met dank aan dr. Willy Storms

PSA: THE NEVER ENDING STORY?

Screening for prostate cancer with prostate specific antigen (PSA) remains highly controversial because it is unclear whether the benefits of reduced prostate cancer mortality offset the harms of overdiagnosis and overtreatment. Given this uncertainty, most high income countries have chosen not to implement a national programme of prostate cancer screening, but allow men to obtain a PSA test after a conversation with their physician.

Countries that have adopted screening policies based on shared decision making have seen high rates of PSA testing, particularly among men 70 years or older, who are particularly prone to overdiagnosis but do not benefit from screening. This is one of the reasons why opportunistic screening results in only a small reduction in cancer specific mortality. Moreover, relying on shared decision making to guide PSA testing has led to an uneven distribution, with higher rates of PSA testing among those who are wealthier and more educated.

In 2022 the European Union recommended that organised screening programmes should be extended to prostate cancer. We argue that high income countries should either implement a comprehensive risk based approach to PSA testing, one that is designed to reduce overdiagnosis and overtreatment, or discourage PSA testing through a clear recommendation against screening, along with policies that make it hard to obtain a test without defined urological indications.

Informed choice approach drives high rates of testing

High income countries that have made PSA testing available to men who request it after shared decision making with their physician now have a high prevalence of PSA testing with an inappropriate age distribution (table 1). In the UK, men aged 80-89 are twice as likely to get a PSA test as men in their 50s. In France, 30% of men aged over 40 get an annual PSA,with the highest incidence of PSA testing in men over 70. Italy and Germany also have high rates of PSA testing with around half of men aged over 70 having annual PSA. Ireland has particularly high rates of PSA testing, with 500000 PSA tests performed each year in a population of 600000 men of screening age.

High rates of PSA testing from “informed choice” policies in high income countries have led to harm from overdiagnosis and overtreatment. In the UK, prostate cancer incidence has increased by about 50% since PSA testing became available in the early 1990sto a current total of 52000 cases a year. Around 25-50% of men who have prostate cancer detected after PSA testing would have lived out their natural lives without a prostate cancer diagnosis,suggesting that overdiagnosis occurs in about 10000 men in the UK every year.

A key problem is that, in current routine care—and despite guidelines to the contrary—most men with an abnormal PSA result have prostate biopsy, even though only a minority will have aggressive prostate cancer. Furthermore, most men with biopsy detected cancers have either surgery or radiotherapy (with or without androgen deprivation therapy) even if they have low risk tumours that are unlikely to cause cancer related morbidity or mortality. Prostate surgery and radiotherapy are both associated with a high risk of long term urinary, erectile, and bowel dysfunction, while androgen deprivation causes numerous side effects such as fatigue and loss of libido during treatment and increases the long term risk of cardiovascular events.

Table 1: National recommendations on prostate specific antigen (PSA) screening compared with empirical data on PSA testing in the population*

Country	Recommendation	Current use of PSA testing
Australia	"The PSA test is not suitable for population screening … We encourage men to speak to their doctor so they can make an informed choice about prostate cancer testing"	High rates of PSA screening (around 20% of men screened annually, about 50% in lifetime) with comparable rates in men aged 75-84 and 45-74
Canada	No population based screening. Policies vary by province. In some, the nationalised health insurance system does not pay for PSA in asymptomatic men; in others testing is free	40-60% of men of screening age have annual testing, with a 50% rate in men aged ≥70.89 Lower rates of testing in people from minorities and those on low incomes or less well educated
France	No national screening programme, but PSA testing available after shared decision making	Around 30% of men ≥40 have had a PSA test in past year. Highest testing rate in men aged over 70, with about 50% having at least one test and 20% having more than 3 tests over three years
Germany	No national screening programme. PSA testing has not been approved by the German statutory health insurance and patients have to pay themselves	Around 75% of men >55 have been tested.14 Around half of PSA tests are in men aged over 69
Ireland	No national screening programme but PSA testing available after informed consent and shared decision making16	Close to 500000 PSA tests a year17 with an eligible population of around 60000018
Italy	No national screening programme†	About 75% of men >50 have ever had a PSA test. Highest prevalence of annual testing (roughly 50%) in men aged ≥70
Sweden	"The health system should not offer screening for prostate cancer with PSA."† Population based PSA testing programmes are being piloted in some regions	About 70% ever had a PSA test with highest rates in men aged 70-89 (30%-50% over 2 years)
Switzerland	No national screening programme†	Around 70% of have been tested, with 40% in the past two years. High rates in older men (around 50% in past 2 years for age ≥70). Testing positively correlated with education, income, and urban location
UK	Screening for prostate cancer is currently not recommended. The NHS has an "informed choice programme": "If you're aged 50 or	Strong regional variation in PSA testing and high inequity, with testing inversely correlated with economic deprivation. Testing rates about

Country	Recommendation	Current use of PSA testing
	over and decide to have your PSA levels tested after talking to a GP, the NHS will pay for it"	twice as high in men aged 70-90 (about 40% in past years) as in men aged 50-59 (about 20%)
US	"For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)-based screening for prostate cancer should be an individual one"	About 30% of men receive PSA test each year. Highest rates for men aged 70-79 and considerable screening (~30%) in men aged ≥80. Clear evidence of disparities with screening rates associated with education and insurance status and lower rates among people from minority groups

- ** Note that most studies were unable to distinguish PSA used for screening versus PSA used for clinical reasons, such as follow-up in a patient with prostate cancer. However, the latter will be a small minority of the total and hence are unlikely to influence estimates importantly.*
- *† It is hard to find policy documentation that patients can receive PSA if they request it, but high rates of PSA testing suggest that this is the case.*

Men who are overdiagnosed thus often experience treatment harms without receiving any benefit.
Approaches to PSA testing that rely on people making an informed choice are likely to reflect and reproduce health inequities in preventive healthcare. Data from Canada, the US, and Switzerland suggest PSA testing is inversely associated with income and education; in Canada and the US, PSA testing is less common in people from ethnic minorities. In the UK and Switzerland, rates of PSA testing are lower in economically deprived areas. Although the effects of disparate rates of PSA testing on health outcomes are still unclear, countries should decide who gets offered screening based on a risk assessment rather than leaving it to individuals.

Advantages of a comprehensive, risk based, prostate cancer detection programme

Policy making bodies that advocate for an informed choice or shared decision making model of PSA testing, typically frame their recommendations as contrasting with population based screening. This is generally defined as PSA testing being structured in a similar way to national mammography or colonoscopy programmes: the screening test is provided by a government run body at standardised intervals with follow-up of abnormal results handled within the national health system. A 2012 statistical modelling study based on evidence from randomised trials suggests that this sort of universal PSA testing programme for men aged 55-69 would reduce prostate cancer mortality by 9 per 1000 men but at the cost of 16 quality-of-life adjusted years per 1000 as a result of harm from overdiagnosis and overtreatment.

A comprehensive, risk based prostate cancer detection programme based on best evidence on how to use PSA testing and manage subsequent diagnostic follow-up and treatment

could reduce overdiagnosis and overtreatment. Such a programme would restrict testing to men (and those not identifying as male but who have a prostate) aged 50-70, define testing intervals by PSA levels, stop testing early for those with lower PSA, offer biopsy only to those identified as at high risk of aggressive disease after a secondary test (such as magnetic resonance imaging (MRI) or blood markers), and limit treatment to those with high Gleason grade tumours.The programme would also have a clear algorithm specifying how these approaches would vary for those at high risk (eg, having a BRCA gene mutation or strong family history).

Such a programme would start by defining, identifying, and inviting eligible people for PSA testing. Management of abnormal results and any subsequent treatment would need to be monitored to ensure protocols were followed (eg, confirmatory or secondary testing with MRI in men with raised PSA levels), rather than passively expecting guidelines to be followed; indeed, our current problems stem largely from practices that go against guideline recommended care. Although in the UK most men have a biopsy only after MRI, this is not always the case in other countries, and other elements of the clinical pathway, such as treatment, also need standardisation. As in current informed choice programmes, shared decision making would still take place before testing.

Swedish regional health authorities are piloting a screening programme using this approach. Prevention of overtreatment is not formally part of the programme because Sweden already has extremely high rates of active surveillance, whereby patients with low risk prostate cancer are monitored and start active treatment only on evidence of more aggressive disease. An early randomised evaluation of the Swedish pilot found use of MRI testing before biopsy led to a >50% reduction in overdiagnosisof low grade prostate cancer without a significant difference in the detection of high grade disease.

A comprehensive prostate cancer early detection programme that carefully manages not just testing, but also biopsy and subsequent treatment, could substantially reduce the harms of overdiagnosis and overtreatment that have accompanied PSA screening. About 40% of overdiagnoses currently occur in men aged over 70. The use of MRI or secondary markers to determine biopsy in men with raised PSA levels has been shown to reduce both biopsy rates and the overdiagnosis of low grade cancer. In one study, patients with raised PSA levels randomised to biopsy only if they had positive MRI findings had a 30% reduction in the rate of biopsy and a 50% reduction in the overdiagnosis of low grade cancer compared with those randomised to routine biopsy, without reducing the number of aggressive cancers detected.50 Use of active surveillance reduces treatment rates by 50% or more in men diagnosed with low grade disease.

Most of the benefit of PSA testing on prostate cancer mortality would be retained in a comprehensive, risk adapted early detection programme because best evidence suggests screening older men is ineffective, men who have negative findings in secondary tests such as MRI or blood markers have extremely low mortality from prostate cancer, and conservative management of men with low risk disease does not increase the risk of death from prostate cancer.

Moreover, in what might be the central paradox of a PSA based prostate cancer screening policy, implementing a national risk based programme would typically reduce the number of tests compared with the current model. In one risk adapted screening approach,men with initially low PSA levels, constituting about half of the population, would have their PSA tested only three times during their lives, with most others getting tested only every 2-4 years. If implemented in Ireland, for instance, such a programme could reduce the number of PSA

tests by at least half compared with contemporary practice. One of the few countries that has implemented a national PSA based programme for early detection of prostate cancer is Lithuania. This has led to a near 80% drop in PSA testing in men aged over 70, the age group for whom PSA screening is most likely to lead to harm and least likely to lead to benefit. An organized early detection programme may also reduce ethnic, socioeconomic, and regional inequalities. For example, in the Swedish randomised trial of PSA testing, reductions in prostate cancer mortality were greater for those with lower educational levels than for those with higher educational levels.Indeed, one of the key benefits of a risk based approach is that it allows better targeting to those at highest risk compared with current informed choice approaches, which are sensitive to affluence and education, as well as undue influence from media coverage, such as celebrities telling their prostate cancer stories.

Restricting access to PSA testing

A reasonable alternative to a comprehensive, risk based prostate cancer early detection programme, is a clear recommendation against PSA screening along with a policy that the PSA test could only be offered by a urologist to patients presenting with urological symptoms, albeit with a possible exception for men at high risk, such as BRCA mutation carriers. This would mean asymptomatic men would not be able to have PSA testing. Such an approach may require governments or public health insurers to do more than refuse reimbursement for the PSA test. For instance, in Germany, PSA tests offered in primary care are not reimbursed by the public health insurance system, yet 75% of German men of screening age have had a PSA test, probably because the test is inexpensive. Specific policies or other mechanisms whereby a national health system could restrict PSA testing are largely untested and would require further research.

Maximising benefit, reducing harm

Although we believe that early detection of prostate cancer should involve shared decision making, the current approach of determining testing by shared decision making has resulted in the worst possible practical outcome of high levels of PSA testing and medical harm, with minimal benefit and inequity. To make better use of PSA testing, policy makers should choose between a comprehensive, risk adapted approach that is specifically designed to reduce overdiagnosis and overtreatment, or restricting PSA testing to people referred to urologists with symptoms. That choice will need to take into account wider patient and public perspective, as well as health economic concerns.

Key messages

- Most high income countries have chosen not to implement a population based prostate cancer screening programme but instead allow men to obtain a PSA test if they wish
- These policies have led to paradoxically high rates of PSA testing, clear medical harm, scant benefit, and inequities
- A national comprehensive, risk based, prostate cancer detection programme that is carefully designed to reduce overdiagnosis and overtreatment would reduce harm, increase benefit and be more equitable
- An alternative approach to reducing harm is to restrict PSA testing to those referred to urologists for symptoms

https://www.bmj.com/content/381/bmj-2022-071082

Met dank aan dr. Leslie Vander Ginst

Bronnen

THE LANCET JAMA The Journal of the American Medical Association ACP thebmj Prescrire

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