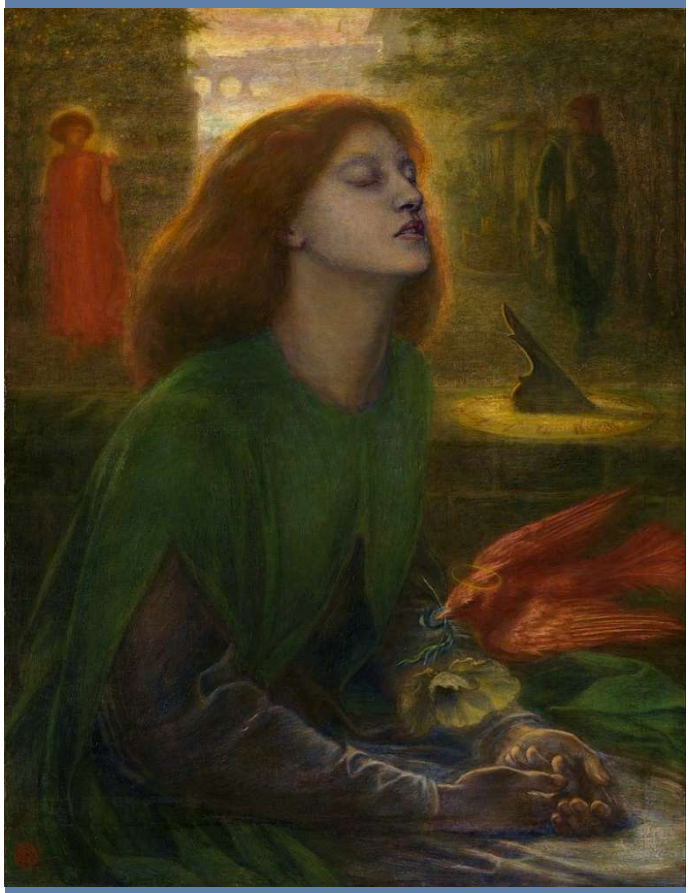

DANTE GABRIEL ROSSETTI
Beata Beatrix 1864

MCH **DIGEST**
WETENSCHAPPELIJKE TIJDINGEN

Een maandelijkse wandeling door de medische literatuur

verschijnt maandelijks – **Juni 2023**

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Inhoudstafel

Ratrace als cultus

Had de slak bij het bloemenplanten voorzichtig opzijgezet. Tot mijn verbazing vond ze de weg terug, met een zigzaggend slijmspoor. Met een slakkengangetje weliswaar. Maar ze bereikte haar doel. Traag gaat dus ook.

Al generaties lang klagen mensen erover dat het leven zo druk is. Maar stel u voor dat mensen uit de negentiende eeuw de ratrace van vandaag, in de westerse wereld tenminste, zouden meemaken.
En toch is het aantal betaalde werkuren sinds die tijd fors teruggelopen. Nu presteert een gezin gemiddeld zeventig uren betaalde arbeid per week. Maar dan dient ook gepresteerd. Werkgevers zijn niet dol op uitlopende koffiepauzes en tateren tijdens de dure werkuren. Zij eisen efficiëntie.

Werknemers passen zich vaak/soms aan in die gedachtegang. Zij zeggen wat graag dat het toch zo druk is. Drukte als statussymbool, dat de illusie geeft belangrijk te zijn, zelfs onontbeerlijk. Past soms in de bedrijfscultuur.

Ook dokters zijn gevoelig aan dat imago. Er is een tijd geweest dat het not done was tijdig op een vergadering te komen. Druk, druk, druk collega's! Kortom, drukte als symbool van geslaagd te zijn in het leven. Dat verandert stilaan naar dokters die organisatie, zelfzorg en vrije tijd/werkbalans willen uitstralen.

In de negentiende eeuw was net heel veel tijd hebben een statussymbool! De baron die rondreed in zijn koets zag het labeur van de knechten op het veld en etaleerde wat graag dat hij niet hoefde te werken.

Die vrije tijd zag er ook wat anders uit. De werkende mens was alleen vrij op 'de dag des Heren'. Die besteedde hij aan de fanfare, de voetbal, toneelvereniging en de dorpscafés. Of op de stoel voor de deur om met de buren te kouten. Een dagje naar zee of naar het museum waren er niet bij.

Wat is dan de laatste decennia zo veranderd? Het consumptiegedrag en de vrijetijdsbesteding.

De consumptie is sinds de golden sixties gigantisch gestegen. Kan me inbeelden dat overgrootouders vroeger een tafel, bed en kachel voldoende vonden om in het huwelijksbootje te stappen. Nu zijn de behoeften en de verwachtingen van de jonge koppels ietwat bijgesteld. De toegenomen gemiddelde welvaart is een goede zaak natuurlijk. Maar koken kost geld.

Waar men vroeger met één verdiener diende toe te komen, zijn de gezinnen met tweeverdieners niet meer weg te denken. Niet alleen door de emancipatie, maar zeker ook uit noodzaak, wil men het redden met huidige lonen en consumptienood. Aangezwengeld door de marketing.

Alhoewel de gemiddelde tijd die aan betaalde arbeid wordt besteed afneemt, hebben velen het gevoel dat ze niet kunnen doen wat ze allemaal zouden willen doen.
Maar het vrijetijdsaanbod is enorm gestegen. Niet van alles kunnen proeven creëert bijna een schuldgevoel. En groot aantal sportmogelijkheden, films, concerten, toneel, festivals, citytrips, vriendschappen onderhouden, de kinderen van hot naar her brengen…. Het vraagt zowaar een aparte vrijetijdsagenda.

En dan vergeet ik nog de sterk toegenomen prikkels voor wie op (a)sociale media zit, zoals fakebook en tetter. Voor velen niet alleen een belangrijke bron van tijdverlies, maar ook verstoorders van de concentratie. Sinds corona is de vaak opgedrongen schermtijd gemiddeld met 35 minuten toegenomen.

De mens is een 'homo economicus' geworden, vermalen in een marktsysteem dat gebruikt en verbruikt. 'Work hard, play hard' past perfect in dat plaatje, maar willen we dat?

Tijdens onze paasvakantie las ik een boek, nochtans aangeraden door een belezen vriend, waarvan ik het op de heupen kreeg omdat het zo traag vooruit ging. Ben ik in die ratrace dan ook verleerd op mijn rug in het gras te liggen en naar de voorbijschuivende wolken te kijken? Jammer is dat.

Dr. Karel DE KOKER
bestuurder MCH

Nascholingsprogramma academiejaar 2022-2023

Webinars

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

15.06.2023 Titel: Wat de huisarts anno 2023 moet weten over (jong)dementie
Spreker: prof. dr. Mathieu Vandenbulcke en prof. dr. Jos Tournoy
Moderator: dr. Jo Lissaerde

Fysieke nascholingen

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

20.06.2023 Titel: Goed in je vel als zorgverlener*
Spreker: Els Deboutte, coach, trainer & mede-oprichter bij Make me fly
*zal doorgaan in MCH Leuven, niet geaccrediteerd

P.U.K. – Druivenstreek vzw

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

22.06.2023 Titel: Urgenties in de oftalmologie
Spreker: dr. Nancy Verdonck en prof.dr. Karel Van Keer
Moderator: dr. Noël Mortier

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

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

Orthopedie

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

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

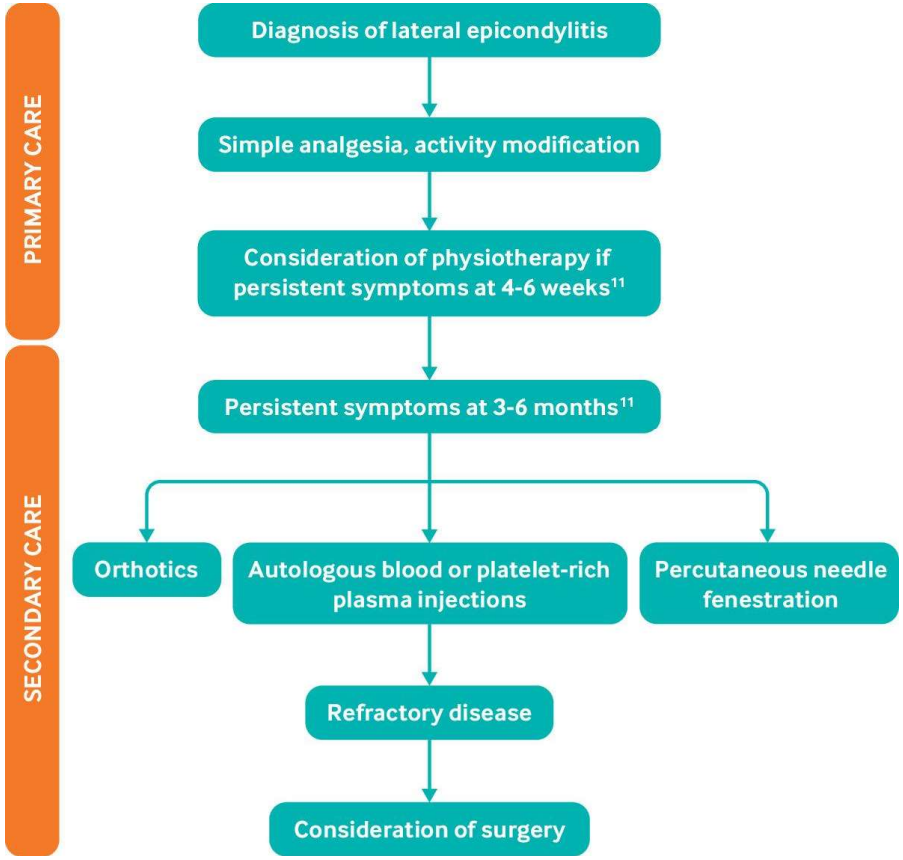
- Radial tunnel syndrome—posterior interosseous nerve compression causing pain on the posterolateral aspect of the arm. It may be worse at night and associated with weakness on wrist or finger extension
- Arthropathy—osteoarthritis in the elbow commonly affects the radiocapitellar joint, and can lead 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.

PROPOSED 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.

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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.

Table 1 FDA approved medications for bipolar disorder

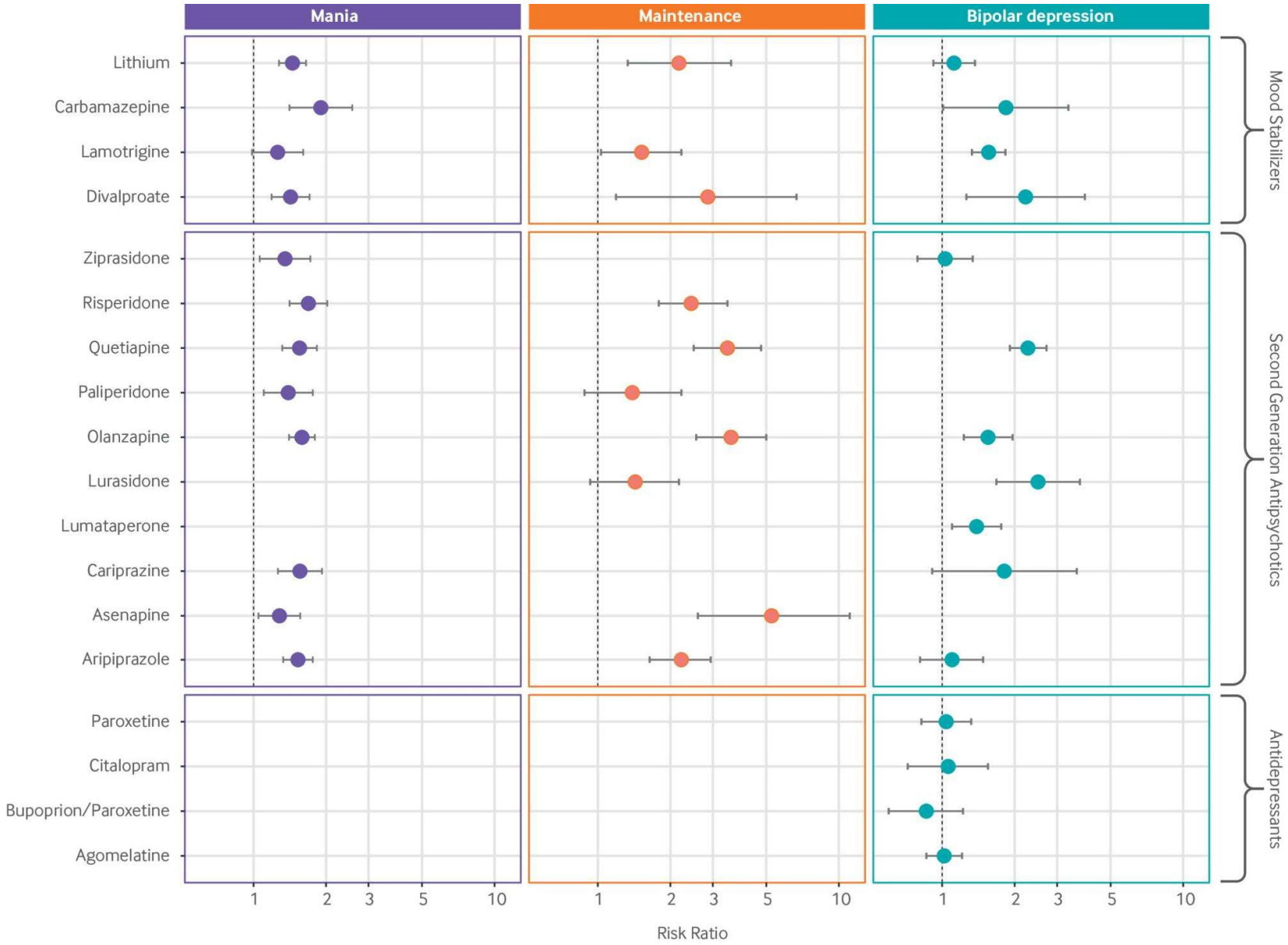
Drug	Dosage	Notes	Main side effects
Treatment of mania and mixed episodes			
Lithium	Initial dose 300 mg twice a day Titrated to blood level of 0.8-1.2 mEq/L	• Approved 1970 • Most widely studied mood stabilizer • Blood levels essential for titration and maintenance	• Weight gain • Polyuria • Tremor • 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	• Approved 1973 • Only typical antipsychotic	• Extrapyramidal symptoms • Sedation

Drug	Dosage	Notes	Main side effects
	Target dose 200-600 mg	approved for mania • Rarely used in current practice	• 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 • 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
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	• Somnolence • Dizziness • Weight gain

Drug	Dosage	Notes	Main side effects
		associated with BD-I and BD-II	• 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
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	• QT interval prolongation

Drug	Dosage	Notes	Main side effects
		lithium or divalproate	
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

FDA=Food and Drug Administration.


Mania
Maintenance
Bipolar depression
Lithium
Carbamazepine
Lamotrigine
Divalproate
Ziprasidone
Risperidone
Quetiapine
Paliperidone
Olanzapine
Lurasidone
Lumataperone
Cariprazine
Asenapine
Aripiprazole
Paroxetine
Citalopram
Bupoprion/Paroxetine
Agomelatine
Mood Stabilizers
Second Generation Antipsychotics
Antidepressants
1
2
3
5
10
Risk Ratio

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

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.

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 clinical 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.

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Urologie

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.

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 over and decide to have your PSA levels tested after talking to a GP, the NHS will pay for it"	Strong regional variation in PSA testing and high inequity, with testing inversely correlated with economic deprivation. Testing rates about 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.

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.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

Toemaatje

NACHTELIJK ZWETEN

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.

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

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 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.

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.

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
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,	Blood culture	One set: 73-80% sensitivity for bacteraemia,

Condition	When to consider testing	What initial tests to order	Test characteristics
	embolic stigmata in extremities		may be more sensitive in endocarditis
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 ≥0.43×10^9/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.

What further investigations should be requested in primary care?

For patients with laboratory evidence of active inflammation without clear aetiology from initial work-up, or if malignancy or occult infection (such as parenchymal abscess) is suspected, it is reasonable to proceed with cross sectional computed topography (CT) imaging in primary care.

Reducing unnecessary testing

- Because of the non-specific nature of night sweats, there are a myriad of potential tests that a clinician could consider ordering at the initial evaluation. We recommend aiming to avoid a “one size fits all” diagnostic approach. For example, patients presenting with night sweats do not need an initial evaluation for lymphoma if they do not have other supporting clinical features or risk factors.
- Additionally, testing can often be done in a stepwise fashion. For most patients presenting with night sweats, the initial diagnostic evaluation should include laboratory testing and potentially chest radiography. Most patients presenting with night sweats do not initially warrant CT imaging or TTE, though these can be reconsidered if symptoms are persistent or if the initial work-up is suggestive of occult malignancy or infection. However, in areas of the world where infections such as tuberculosis have high incidence, a presumptive diagnosis may be possible based on medical history and symptoms alone, and treatment may be initiated with close monitoring before pursuing any diagnostic testing.

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Met dank aan dr. Lesley Vander Ginst

FREQUENT LIKKEN VAN DE LIPPEN: MOGELIJKE GEVOLGEN

Liplikeczeem (lip licking dermatitis) ontstaat door het frequent likken van de lippen en de omliggende huid en is dus een vorm van contacteczeem: door herhaald contact met speeksel raakt de huid beschadigd en vervolgens ontstoken.

Etiologie en pathogenese

- Men kan in de regel spreken van een vicieuze cirkel:
  - Begint bij een droge huid die patiënt ertoe beweegt om de lippen veelvuldig met speeksel te bevochtigen.
  - Er volgt een beschadiging van de huid door het vocht en de verteringsenzymen in het speeksel.
  - De huid raakt uitgedroogd en geïrriteerd en dat zet de patiënt aan om nog meer te likken.
- Er zijn er die dit veelvuldig likken als een tic beschouwen en daarom wordt het fenomeen wel eens *'tic des lèvres'* genoemd.
- In de wintermaanden, wanneer de huid droger is, lijkt liplikeczeem meer voor te komen.

Differentiaaldiagnose

- Hiertoe behoren dermatitis perioralis, perlèche, atopisch eczeem en impetigo.
- Een geïsoleerde contactallergie rond de mond, bvb. in reactie op bestanddelen van tandpasta, kan soms ook sterk op liplikeczeem lijken:
  - Bij liplikeczeem: hier zijn uitsluitend de lippen en de direct omliggende huid aangedaan, net tot daar waar de tong bij kan komen.
  - De huid is bij de andere aandoeningen meestal ook buiten het bereik van de tong beschadigd en vaak is er juist rond de lippen een zone niet aangetast.

Epidemiologie

- Liplikeczeem is in de literatuur bij patiënten van alle leeftijden beschreven, maar ziet men toch het vaakst bij kinderen:
  - Liplikeczeem lijkt zich ook vaker te ontwikkelen bij patiënten met een angststoornis of depressie en patiënten met een mentale beperking.
  - Er zijn ook aanwijzingen dat de aandoening vaker bij vrouwen dan bij mannen voorkomt.
- Atopie lijkt een predisponerende factor te zijn en dat komt mogelijk omdat atopische patiënten vaak al een wat drogere huid hebben.
- Liplikeczeem wordt in de huisartsenpraktijk geregistreerd onder ICPC-code S88 (Contacteczeem / ander eczeem) = een verzamelcode:
  - In de leeftijdscategorie 0-1 jaar is de incidentie 43,5 per 1000 kinderen per jaar.
  - Bij de leeftijd van 1 tot 14 jaar bedraagt de incidentie 20-30 per 1000 kinderen per jaar.
- Het is wel niet bekend welk gedeelte hiervan liplikeczeem betreft.

Waarmee komt de patiënt ten berde?

- Ze komen vaak met gevoelige, branderige of pijnlijke lippen, en soms met jeuk.
- Er zijn er sommige – of hun ouders – die aangeven dat ze het eczeem cosmetisch storend vinden.

Anamnese

- Men moet vragen naar herhaaldelijk likken van de lippen.
- Verder een bevraging in verband met atopische eczeem, stress of overbelasting en allergieën.
- Bij aanwezigheid van crustae vraagt men ook of er in de omgeving (klasgenoten, kinderopvang) mensen zijn met impetigo (‘krentenbaard’), en men vraagt ook naar koorts of ziek zijn.

Klinisch onderzoek

- Lokaal onderzoek volstaat meestal:
  - Men ziet bij inspectie van de mond perioraal een scherpbegrensde, erythematosquameuze huiduitslag.
  - De begrenzing hiervan komt overeen met de reikwijdte van de tong.
  - Het eczeem is soms alleen aanwezig op de omliggende huid tot aan het lippenrood.
  - Meestal is het lippenrood echter zelf ook aangedaan.
  - De lippen zijn droog, vertonen kloofjes en soms zijn er bloedlkorstjes.
- Blijft het eczeem langdurig aanwezig, dan kan er hyperpigmentatie ontstaan van de huid:
  - Meestal verdwijnt deze postinflammatoire hyperpigmentatie vanzelf na een paar maanden.
  - Hypopigmentatie kan overigens ook als tijdelijk restverschijnsel optreden.
- Er is soms sprake van impetiginisatie van het eczeem:
  - Er zijn in dit geval honinggele crustae aanwezig.
  - Er kunnen in zeldzame gevallen ook blaren (impetigo bullosa) aanwezig zijn.
- Bij liplikeczeem is aanvullend onderzoek zelden nodig:
  - Reageert de impetiginisatie niet op AB, dan kan een kweek afgenomen worden.
  - Bedoeling is dan om vast te stellen met welke verwekker(s) het eczeem geïnfecteerd is.

Aanpak

- Informatie:
  - Meest belangrijk is dat de patiënt ophoudt om steeds de lippen te likken.
  - Vertel dus aan patiënt dat likken de klachten uitlokt en in stand houdt.
  - Zeg dat de klachten binnen 4-6 weken vanzelf verdwijnen als de patiënt stopt met likken.
- Zalf:
  - Stimulatie van het genezingsproces kan geschieden door meerdere keren per dag een indifferente zalf, bvb. vaseline, op en rond de lippen aan te brengen.
  - Op die manier vormt de zalf een barrière die voorkomt dat het speeksel de huid verder irriteert en uitdroogt.
  - Blijft de aandoening hardnekkig aanwezig, dan kan men gedurende korte tijd gebruik maken van een lichte corticosteroïdzalf, type hydrocortisonezalf, om uitkomst te bieden, maar meestal is dit niet nodig.
  - Is er impetiginisatie van het eczeem aanwezig, dan kan men starten met een antibiotische zalf, en dan is fusidinezalf de eerste keus.
  - Enkel bij ernstige infecties kan men een oraal AB overwegen.
- Hygiëne:
  - Bij impetiginisatie van het eczeem geldt als belangrijk advies om de nagels kortgeknipt te houden.
  - Verder moet men de handen dan frequent reinigen met water en zeep en het

geïmpetiginiseerd gebied zo min mogelijk aanraken om verspreiding van de bacteriën te voorkomen.

Wanneer verwijzen?

- Is bij liplikeczeem zelden nodig, immers dwangmatig likken is vaak een voorbijgaande tic.
- Soms is echter ondersteuning van een (kinder)specialist gewenst om het gedrag af te leren.
- Bij diagnostische twijfel of bij onvoldoende respons ondanks adequate behandeling is een verwijzing naar de dermatoloog te overwegen.

Preventie en voorlichting

- Het is van belang om de patiënten ervan bewust te maken dat liplikeczeem ontstaat door het veelvuldig likken van de lippen en erdoor in stand wordt gehouden.
- Stimuleer mensen in het sociale netwerk van de patiënt, zoals ouders en onderwijzers, om deze telkens op het liplikken te wijzen als het optreedt.
- De aandoening verdwijnt doorgaans binnen enkele weken volledig met adequate instructies en begeleiding (niet likken aan de lippen en meermaal daags insmeren met vaseline).
- Tenslotte: gecontroleerd onderzoek naar de behandeling van lipeczeem is er niet te vinden, de adviezen berusten dus op consensus en ervaring.

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VERSTANDELIJKE BEPERKING EN NOOD AAN ONCOLOGISCHE BEHANDELING

Er bestaan weinig richtlijnen en indicatoren die helpen bij de vormgeving van passende oncologische zorg voor mensen met een verstandelijke beperking, hoewel er verschillende valide redenen zijn waarom deze zorg voor deze groep anders is.

Deze groep is daardoor vooral afhankelijk van de affiniteit en ervaring van de zorgverlener, iets wat bijdraagt aan een ongelijke zorg. Vraag is dan ook hoe deze situatie kan verbeterd worden.

Demografie verstandelijke beperking

- Betreft een ontwikkelingsstoornis die bij 1 tot 3% van de bevolking voorkomt en dat gaat in Nederland om ongeveer 400.000 personen, waarvan de helft langdurige zorg en ondersteuning ontvangt:
  - Wanneer iemand een beperkt cognitief vermogen heeft (IQ < 70) in combinatie met beperkingen in (sociaal) functioneren, dan is er sprake van een verstandelijke beperking.
  - De beperking is hierbij ontstaan op de kinderleeftijd.
- Meest voorkomende oorzaken van een verstandelijke beperking zijn de volgende:
  - Chromosiale of andere genetische afwijkingen (tot 60% van de gevallen), geboortedefecten (30%) en aanlegstoornissen (10%).
  - In de praktijk: van meer dan de helft van de personen met een verstandelijke beperking is de oorzaak niet bekend, omdat er geen of beperkte diagnostiek verricht is om de oorzaak te bepalen.
- Door gezondheidsproblemen die met de beperking samenhangen zijn mensen met een verstandelijke beperking vaak kwetsbaar:
  - Gaat o.a. om motorische problemen, epilepsie en problemen met de luchtwegen, spijsvertering en stofwisseling.
  - Vroege veroudering, late herkenning van ziektesymptomen en moeizame toegang tot zorg spelen echter ook een rol.
- Deze combinatie van factoren levert zijn bijdrage voor het feit dat mensen met een verstandelijke beperking gemiddeld 15 jaar korter leven dan mensen zonder verstandelijke beperking.
- Het is nog niet volledig duidelijk welke rol kanker hierin speelt.

Risico's op oncologische aandoeningen

- Bij mensen met een verstandelijke beperking is de exacte prevalentie van kanker moeilijk te bepalen, maar verschillende subgroepen hebben wel een verhoogd risico op kanker:
  - Leukemie en testiscarcinoom bij mensen met het syndroom van Down zijn hiervan voorbeelden.
  - Dat geldt ook voor hersentumoren bij neurofibromatose type I.
- In bepaalde subgroepen komen niet-genetische risicofactoren, zoals een ongezonde leefstijl en roken – afhankelijk van de mate van beperking – vaker voor.
- Aan bevolkingsonderzoeken nemen mensen met een verstandelijke beperking ook minder goed deel.
- Onderzoek in Nederland levert de volgende bevindingen:

- Mensen met een verstandelijke beperking komen minder vaak naar het ziekenhuis voor oncologische zorg dan mensen zonder deze beperking.
- Nochtans is de kans voor overlijden groter voor die eerste groep, iets wat men namelijk ziet bij kankersoorten waarvoor bevolkingsonderzoeken bestaan.

- Er zijn ook internationale onderzoeken die aantonen dat diagnoses in deze groep – in ieder geval bij colon- en mammacarcinoom – in een later stadium gesteld worden dan bij de algemene bevolking.
- In Nederland verloopt vervolgonderzoek hiernaar nog.

Oncologische behandeling: wat zegt de literatuur?

- Er is recent literatuuronderzoek verricht om beter inzicht te krijgen in de wetenschappelijke literatuur over de oncologische behandeling van patiënten met een verstandelijke beperking:
  - Over de besluitvorming of behandeling van kanker bij patiënten met een verstandelijke beperking werden er 90 artikels gevonden.
  - 78 van deze 90 artikels – de meerderheid dus – gingen over casuïstiek.
  - Geen van de artikels betrof een klinische trial of andere interventiestudie.
- Er was onvoldoende beschrijving van de achtergrond van de verstandelijke beperking:
  - In een kwart van de artikels (23/90) werd er geen oorzaak vernoemd van de verstandelijke beperking bij de patiënten die beschreven werden.
  - In meer dan de helft van alle artikels (53/90) werd de ernst van de verstandelijke beperking niet toegelicht.
- Bij deze groep beschreven de geïncludeerde artikels tenminste 6 verschillende syndromen als oorzaak van een verstandelijke beperking en 12 verschillende kankersoorten.
- Bij aanpassing van de reguliere behandeling in de beschreven casussen was er in de meeste gevallen sprake van verlaging van de dosis of volledig weglaten van radio- of chemotherapie:
  - Als reden voor de aanpassingen werd de verstandelijke beperking van de patiënt het vaakst opgevoerd (90%).
  - Hierbij werden specifiek genetische kwetsbaarheid of gedragsproblemen genoemd.
  - Fysiologische factoren werden ook gemeld,zoals leeftijd, respiratoire problemen en tumorlocatie.
- Niet-medische redenen hadden met juridische en ethische aspecten te maken rond wilsbekwaamheid en beslisbevoegdheid:
  - Zo was er één cross-sectionele studie die rapporteerde dat bij geen van de patiënten met een verstandelijke beperking toestemming verkregen werd voor adjuvante chemotherapie bij chirurgische behandeling voor borstkanker.
  - Dit gebeurde ongeacht de ernst van de beperking.
  - Zo'n 30% van de artikels waarin een behandelaanpassing beschreven werd gaf geen onderbouwing voor de gemaakte aanpassingen.

Casus betreffende passende zorg in de praktijk

- Gaat om een ernstig verstandelijk beperkte vrouw bij wie een mammacarcinoom vermoed werd:
  - Omdat patiënte zich verzette tegen een mammografie werd in het ziekenhuis een echografie uitgevoerd.
  - Er volgde een multidisciplinair overleg en hieraan nam de arts voor verstandelijk gehandicapten (arts VG) van de patiënt deel.
  - Besloten werd om onder algemene anesthesie een biopsie uit te voeren met directe beoordeling van het biopt.
  - Na bevestiging van de diagnose werd in dezelfde sessie een borstamputatie met okselkliertoilet uitgevoerd.
  - Patiënte accepteerde wel adjuvante chemotherapie en samen met het multidisciplinaire team werd gezocht naar een acceptabele follow-up.
- Patiënte gaat inmiddels weer naar de dagbesteding en fietst haar rondjes over het instellingsterrein.

Waar kan men relevante adviezen vinden?

- Er werd in het geval van de casus gezocht naar passende zorg voor de patiënte:
  - Er is vooral gebruik gemaakt van kennis over de kenmerken van de patiënte om hier invulling aan te geven.
  - Men gebruikte ook de creativiteit van het multidisciplinaire behandelteam.
- Er bleek uit de genoemde literatuurstudie al dat de literatuur weinig houvast biedt voor praktijksituaties waarin men overweegt om de oncologische behandeling van een patiënt met verstandelijke beperking aan te passen:
  - De bestaande oncologische behandelrichtlijnen bieden ook weinig houvast, mede als gevolg van de beperkte wetenschappelijke kennis.
  - Komt omdat daarin geen specifieke aandacht is voor patiënten met een verstandelijke beperking.
- In de richtlijnen die ontwikkeld zijn voor palliatieve zorg en voor zorg rond het levenseinde bij mensen met een verstandelijke beperking zijn er wel relevante adviezen terug te vinden:
  - In feite gaan deze richtlijnen over een fase in het zorgproces en niet over specifieke aandoeningen.
  - Toch beschrijven ze praktische juridische en ethische aspecten van besluitvorming die ook in de oncologische behandelsetting van belang zijn.
  - Ook geven deze richtlijnen specifieke adviezen over het bepalen van de wilsbekwaamheid en het betrekken van naasten bij de besluitvorming.

Wilsbekwaamheid van een patiënt

- Deze kan variëren in de loop van de tijd:
  - Iemand met een verstandelijke beperking kan voor een simpele diagnostische verrichting wilsbekwaam zijn.
  - Voor de beslissing over een ingrijpende behandeling geldt dit mogelijk niet.
  - Daarom spelen begeleiders en familie een belangrijke rol, ook als ze niet de formele rol van wettelijk vertegenwoordiger hebben.
- In het verleden kunnen naasten al bepaald hebben wat de grenzen aan de behandeling zijn, of een niet-behandelsbeleid afgesproken hebben:

- Er kunnen tegelijkertijd misverstanden bestaan over de impact of tolerantie van de behandeling.
- Bijkomende psychische problemen of gedragsproblemen kunnen ook een reden zijn om behandelingen niet aan te bieden.
- Kan bvb. als de veiligheid van de behandeling of zorgverleners in het gedrang is, maar hierbij is maatwerk vereist.

- Door de Nederlandse Vereniging Artsen Verstandelijk Gehandicapten (NVAVG) en de Vereniging Gehandicaptenzorg Nederland (VGN) worden verschillende naslagwerken aangeboden met nadere uitwerking rond de vertegenwoordiging van menen met een verstandelijke beperking bij medische besluiten.

Rol voor de arts VG

- Betrokkenheid van een arts VG in het multidisciplinaire behandelteam kan gewenst zijn om passende zorg te creëren:
  - De betrokken zorgverleners moeten hierbij dan wel de verstandelijke beperking herkennen.
  - Dat is namelijk nodig in situaties waarin de arts VG niet de verwijzer is.
- Een afwijkende presentatie van klachten en symptomen kan de zorgverlener op het verkeerde been zetten, als niet bekend is dat de patiënt een verstandelijke beperking heeft.
- Is de beperking wel bekend, dan is er ook alertheid gevraagd, want dan kunnen klachten en symptomen ten onrechte toegeschreven worden aan de verstandelijke beperking in plaats van aan een bijkomende aandoening zoals kanker:
  - Voorbeeld ter zake: pijn bij kanker kan zich bij iemand met een verstandelijke beperking uiten in gedragsverandering.
  - Wordt de gedragsverandering toegeschreven aan de beperking, dan kan dit adequate herkenning en bestrijding van kankersymptomen in de weg staan.
- Bij de juiste interpretatie van klachten en gedrag kan een arts VG helpen en hij kan de vertaalslag maken naar de impact van de behandeling voor de patiënt:
  - De arts VG kan daarnaast een inschatting maken van hoe en in welke mate de patiënt betrokken wordt bij de besluitvorming en 'advance care' gesprekken voeren.
  - De arts VG kan vanuit de etiologie van de verstandelijke beperking de oncoloog ook adviseren over mogelijk te verwachten complicaties.

Besluit

- Hoewel de exacte prevalentie van kanker bij mensen met een verstandelijke beperking onbekend is, zijn er aanwijzingen dat deze groep moeizamer toegang heeft tot oncologische zorg, met als gevolg slechtere uitkomsten.
- Mogelijk kunnen de diversiteit aan onderliggende genetische syndromen, comorbiditeit en bijkomende gedragsproblemen om aanpassing vragen van standaardprocedures en dat kan invloed hebben op alle fases van het oncologisch zorgproject.
- Literatuur én oncologische behandelrichtlijnen bieden weinig houvast voor passende oncologische zorg aan deze kwetsbare groep:
  - Met expertise, creativiteit en geduld van het behandelteam kunnen desondanks acceptabele resultaten behaald worden.

    - Aan onderzoekers dus de taak om het gat in de literatuur te vullen.
- Hierdoor kan kennis over de oncologische behandeling van deze doelgroep toenemen en breder gedeeld worden.

Ned Tijdschr Geneeskd 2 december 2022 pag. 8-12.

Kinderheelkunde

DE PIRS-TECHNIEK BIJ KINDEREN MET EEN LIESBREUK

Een van de meest uitgevoerde operaties bij kinderen is een liesbreukcorrectie. De liesbreuken die men bij kinderen vindt, zijn aangeboren, en daarom is er altijd sprake van een laterale liesbreuk.

Als gevolg van een zwakke achterwand van het lieskanaal kan er bij (jong)volwassenen juist een mediale liesbreuk ontstaan.

Welke techniek past men toe?

- Meestal voert men een liesbreukcorrectie bij kinderen uit via een klassieke ('open') chirurgische benadering, maar steeds vaker gebruikt men hiervoor een laparoscopische operatietechniek:
    - Voordeel van een laparoscopische liesbreukcorrectie is dat de lies aan de contralaterale zijde direct kan geïnspecteerd worden.
    - Er moet hier dus geen extra incisie gemaakt worden.
- Er zijn meerdere laparoscopische operatietechnieken ontwikkeld in de loop van de jaren en ze kunnen in twee hoofdgroepen onderverdeeld worden: de intracorporele en de extracorporele techniek:
    - De intracorporele techniek: hier wordt de liesbreuk door een intra-abdominale hechting gesloten.
    - Bij de extracorporele techniek gebeurt dit door een subcutane sluiting.
- Volgt hier een beschrijving van de laparoscopische percutane hechttechniek voor het sluiten van de annulus internus ('percutaneus inguinal ring suturing:PIRS'):
    - Gaat om de minst invasieve laparoscopische operatietechniek , waarbij een extracorporele hechting gebruikt wordt.
    - Men heeft voor deze PIRS-techniek slechts een cameraoptike (diameter: 5 mm, optische breking: 30 graden), een toegangspoort ('trocar') (diameter: 3 of 5 mm), een naald (maat:18 gauge) en hechtdraad (Premicon 0 en PDS 3-0 voor de lus) nodig.

Waarom is er behoefte aan een nieuwe techniek?

- Bij 6-8% van alle kinderen met een unilaterale liesbreuk wordt op een later ogenblik een contralaterale liesbreuk ontdekt, een zogeheten metachrone contralaterale liesbreuk:
    - Deze kinderen krijgen een tweede operatie, narcose en ziekenhuisopname.
    - Gevolg: extra stress en zorgen bij patiënten en de ouders en extra kosten voor de gezondheidszorg.
- De chirurg kan bij een laparoscopische liesbreukcorrectie zonder extra incisie beide liesregio's inspecteren om na te gaan of de processus vaginalis aan de contralaterale zijde open is.
- Is dit het geval, dan kan de processus vaginalis direct gesloten worden:
    - Op die manier blijft de patiënt een tweede operatie bespaard.
    - De extracorporele PIRS-techniek geeft daarnaast mogelijk ook minder complicaties dan de open chirurgische behandeling.

Welke zijn de mogelijke indicaties?

- Bij kinderen van 0-16 jaar met een unilaterale of bilaterale liesbreuk kan de PIRS-techniek toegepast worden.
- De PIRS-techniek wordt momenteel al gebruikt in een aantal academische en niet-academische ziekenhuizen bij kinderen met een primaire liesbreuk of een recidief.

Welk probleem lost men hiermee op?

- Men kan een liesbreukcorrectie uitvoeren via de open chirurgische benadering of een laparoscopische operatietechniek.
- De standaardzorg voor kinderen met een liesbreuk wordt in Nederland momenteel bepaald door de voorkeur en expertise van de behandelende chirurg.
- De laparoscopische PIRS-techniek wordt door een toenemend aantal chirurgen aangewend:
    - Komt omdar deze de mogelijkheid biedt om de contralaterale zijde te inspecteren.
    - Komt ook omdat men een eventuele processus vaginalis direct kan sluiten.
    - Men kan hiermee een metachrone contralaterale liesbreuk voorkomen, welke de meest voorkomende oorzaak is voor een heroperatie na een open liesbreukcorrectie.
- Resultaat: lagere zorgkosten wegens minder operaties, narcoses en opnames, naast minder bezoeken aan de huisarts of de Spoedgevallen omwille van beklemming van een metachrone liesbreuk.
- Verder duurt een operatie met de PIRS-techniek minder lang en geeft mogelijk ook minder complicaties, omdat het de chirurg een beter zicht geeft op de structuren in het lieskanaal.

Wat weet men over de effectiviteit?

- Noch de Nederlandse, noch de Europese richtlijn over de behandeling van kinderen met een liesbreuk laten zien dat er duidelijkheid bestaat over welke nu de beste operatietechniek is, een open of een laparoscopische benadering.
- Er werd onlangs een meta-analyse verricht waarin de uitkomsten van liesbreukcorrecties via een open chirurgische benadering vergeleken werd met laparoscopisch liesbreukherstel:
    - De gegevens van 8 gerandomiseerde studies werden verzameld en die lieten zien dat het aantal complicaties, recidieven en metachrone contralaterale liesbreuken niet statistisch significant verschillen.
    - De operatieduur was ook niet statistisch significant verschillend.
- Uit subgroepanalyse bleek echter dat de laparoscopische extracorporele hechttechniek resulteert in minder complicaties en een kortere operatieduur in vergelijking met de open operatietechniek.
- De superioriteit van extracorporele techniek werd in de meest recente systematische review naar de uitkomst van de intra- en extracorporele laparoscopische (15 studies; n = 3680 kinderen) nogmaals bevestigd:
    - Uit dit literatuuroverzicht bleek dat de extracorporele techniek, die van 1 toegangspoort gebruik maakt, gepaard gaat met minder recidieven en een kortere operatieduur in vergelijking met de intracorporele tabakzakhechting.
    - De verklaring ligt hier voornamelijk bij het feit dat er bij de extracorporele techniek geen gebruik gemaakt wordt van intra-abdominale hechtingen.

De laparoscopische liesbreukcorrectie heeft ook nadelen

- Grootste nadeel:
  - Het is nog steeds niet duidelijk welke van de open processus vaginales daadwerkelijk tot een metachrone contralaterale liesbreuk leidt, waardoor er sprake kan zijn van overbehandeling.
  - Wel is geweten dat men bij ongeveer 9 kinderen de processus vaginalis aan de contralaterale zijde moet sluiten om één metachrone liesbreuk te voorkomen.
  - Bij sommige kinderen leidt preventief sluiten van een open processus vaginalis mogelijk tot dezelfde complicaties als die men kan zien na een primaire liesbreukcorrectie, zoals wondinfectie, (na)bloeding en letsel van de vas deferens en bloedvaten.
- Een ander nadeel is dat de ingreep niet onder spinale anesthesie kan gebeuren, terwijl dit bij baby's wel kan bij een open liesbreukcorrectie.

Hoe moeilijk is het om de techniek aan te leren?

- De techniek heeft een korte leercurve omdat bij de PIRS-techniek niet intra-adominaal gehecht moet worden:
  - Mogelijk is het aantal recidieven na liesbreukcorrectie met de PIRS-techniek aan het begin van de leercurve verhoogd.
  - Het aantal recidieven is echter na het doorlopen van de leercurve gelijk aan dat van de open techniek.
- Uit een recente Portugese studie blijkt dat de leercurve afgerond is na ongeveer 30-35 operaties.
- Vermits er tijdens de opleiding veel ervaring opgedaan wordt met laparoscopische operaties, kan men verwachten dat de leercurve voor de meeste Nederlandse chirurgen korter is.
- De PIRS-techniek is in Nederland in een aantal ziekenhuizen geïmplementeerd, en in al deze ziekenhuizen werd de plateaufase van de leercurve na 10-15 operaties bereikt.

Verwachting voor de toekomst

- De incidentie van een liesbreuk bij kinderen bedraagt 1-2% en zowel de laparoscopische liesbreukcorrectie als de open operatie zijn in Nederland basiszorg.
- De HERNIIA-2-trial is een onderzoek naar de uitkomsten van open liesbreukcorrectie versus de laparoscopische correctie met de PIRS-techniek en moet uitwijzen welke behandeling de beste is voor kinderen met een unilaterale liesbreuk.
- Mogelijk is de PIRS-techniek ook voordelig voor bilaterale liesbreuken:
  - Het resulteert immers in verkorte operatieduur en minder complicaties.
  - Er hoeft ook maar één incisie meer gemaakt te worden.
- Laparoscopische liesbreukcorrectie past men momenteel al toe bij recidiefliesbreuken.

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RA EN LAAG GEDOSEERDE GLUCOCORTICOÏDEN

Men past vaak een behandeling met een glucocorticoïd in lage dosering toe bij patiënten met reumatoïde artritis, maar wegen de voordelen van deze aanpak op tegen de nadelen op lange termijn ?

Een beetje geschiedenis

- Een glucocorticoïd is een steroïd hormoon dat zich kan binden aan de glucocorticoïdreceptor die in iedere lichaamscel aanwezig is:
  - De naam zelf is afgeleid van de rol van glucocorticoïden in het glucosemetabolisme, de aanmaak in de bijniercortex en de steroïdeachtige structuur.
  - Het meest belangrijke humane glucocorticoïd is cortisol.
  - Het is o.a. betrokken bij belangrijke cardiovasculaire, metabole en immunologische processen.
- Samen met 2 chemici isoleerde de Amerikaanse arts Philip Hench als eerste ‘compound E’ – ofwel cortison – uit de bijnierschors en beschreef de spectaculaire ontstekingsremmende effecten, en hiervoor kreeg het drietal de Nobelprijs in 1950.
- Al snel werden de soms ernstige bijwerkingen duidelijk, maar desondanks zijn glucocorticoïden nooit meer van het podium verdwenen.
- Synthetische glucocorticoïden worden ook vandaag de dag veelvuldig gebruikt bij het behandelen van ziekten veroorzaakt door een overactief immuunsysteem, zoals auto-immuunziekten, allergieën, astma en sepsis:
  - Prednison en prednisolon zijn de meest bekende varianten.
  - Glucocorticoïden zijn bij reumatoïde artritis (RA) effectief in het remmen van ontstekingsactiviteit.
  - Glucocorticoïden zijn ook effectief in het beperken van erosieve gewrichtsschade bij RA, zoveel is meermaals aangetoond.

De keerzijde

- Zeker bij toepassing in hogere doseringen kunnen glucocorticoïden ernstige bijwerkingen hebben, daar bestaat geen twijfel over.
- Al meer dan 70 jaar worden deze middelen ingezet, maar toch zijn precieze gegevens over de frequentie van het optreden en de ernst van deze bijwerkingen helaas niet beschikbaar:
  - Komt omwille van het retrospectieve en observationele design van de meeste onderzoeken.
  - Dit resulteert in angst bij patiënten en terughoudendheid bij artsen bij het voorschrijven van corticosteroïden bij niet-levensbedreigende ziekten.
- In de behandeling van RA is er in de afgelopen decennia wel vooruitgang geboekt met de komst van biologicals en ‘targated synthetic’ medicijnen, gericht op een specifieke cytokine of een specifiek enzym:
  - Glucocorticoïden worden in de meest recente behandelrichtlijn van de ‘European League Against Rheumatism’ (EULAR), de Europese beroepsvereniging van reumatologen, enkel genoemd in de context van ‘overbruggen’.
  - Glucocorticoïden worden in het behandelalgoritme tussen haakjes weergegeven.

- Er staat zelfs in de meest recente Amerikaanse richtlijn dat het de voorkeur heeft om helemaal geen glucocorticoïden meer te geven.

De GLORIA-studie

- In de Europese GLORIA-studie staat GLORIA voor 'Glucocorticoïd Low-dose in Rheumatoid Arthritis':
  - 65-plussers met actieve RA werden hierin gerandomiseerd naar de toevoeging van 5 mg prednisolon of placebo aan hun behandeling, en dat gedurende 2 jaar.
  - De gemiddelde ziekteduur van de deelnemers bedroeg ruim 10 jaar en ze kwamen sterk overeen met de gemiddelde patiënt met RA gezien de piekprevalentie van deze aandoening rond de 70 jaar.
- De GLORIA-studie gaf duidelijke resultaten:
  - Toevoegen van prednisolon resulteerde in lagere ziekteactiviteit en minder gewrichtsschade in handen en voeten.
  - Wat betreft de aan glucocorticoïden gerelateerde bijwerkingen zag men in de prednisolongroep vooral een verhoging van het optreden van mild tot matig ernstige infecties (253 vs. 184 infecties in de placebogroep).
- Van diabetes de novo was er geen sprake en symptomatische fracturen kwamen in de prednisolongroep minder vaak voor (4 vs. 2 fracturen).
- Gewichtstoename was een zeldzaam fenomeen.

Bijnierschorsinsufficiëntie

- Dat een lage dosis van 5 mg prednisolon al aantoonbaar effectief is, is een interessant gegeven, en toch geeft deze dosering naar schatting minsten zoveel glucocorticoïde werking als endogeen cortisol onder normale omstandigheden.
- Het is dan ook zo dat langdurig gebruik van een dergelijke lage dosering de hypothalamus-hypofyse-bijnieras onderdrukt:
  - Er is daarom ook bij langdurig gebruik van deze lage dosering een kleine kans op bijnierinsufficiëntie.
  - Dit gegeven is echter in de GLORIA-studie niet gevonden.
- Het lijkt onverstandig om met prednisolon acuut te stoppen.
- Er ontbreken precieze richtlijnen, maar een praktisch advies is om bij stress – zoals ziek zijn of bij kleine chirurgische ingrepen – de dosering tijdelijk naar 15 mg te verhogen.

Besluit

- Uit de Gloria-studie blijkt dat toevoegen van prednisolon 5 mg gedurende 2 jaar een effectieve behandelstrategie is bij ouderen met actieve RA:
  - Dit gebeurt zonder veel risico op bijwerkingen.
  - Weliswaar kwamen infecties frequent voor, maar dat is een risico dat aan de inzet van elk immunosuppressivum kleeft.
- In samenspraak met patiënten kunnen reumatologen de mogelijke voor- en nadelen van de toevoeging van prednisolon afwegen, en hierbij moeten specifieke omstandigheden en comorbiditeiten meegenomen worden.
- Rechtstreekse vergelijkingen met meer moderne, duurdere biologicals zijn niet voorhanden:
  - Een lage dosis prednisolon is echter een aantrekkelijke behandeloptie.
  - Komt door de effectiviteit, gebruiksvriendelijkheid, veiligheid en beperkte kosten.

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NIEUWE POSITIE EN INHOUD VAN I-CATEGORIE IN HET ANTIBIOGRAM

Men geeft in een antibiogram aan welke de gevoeligheid is van een micro-organisme voor of de resistentie tegen potentieel te gebruiken AB en de uitslag ervan wordt bepaald door toepassing van vastgestelde breekpunten.

Uitvoering

- Microbiologische laboratoria in Nederland gebruiken voor het verrichten en interpreteren van gevoeligheidsbepalingen richtlijnen die door de Europese Commissie voor gevoeligheidsbepalingen (EUCAST) opgesteld zijn.
- Aan de aanvrager wordt de uitslag gerapporteerd als een kwalitatieve uitkomstmaat, kwestie van de kans op therapeutisch succes te voorspellen: S (= susceptible, oftewel 'gevoelig'), I (= in de oude definitie 'intermediair gevoelig') of R (= resistent):
    - Recent heeft de EUCAST een belangrijke wijziging doorgevoerd in de betekenis van de I-categorie in het antibiogram.
    - Deze wijziging wordt door de Nederlandse Vereniging voor Medische Microbiologie (NVMM) onderschreven.

Een beetje geschiedenis

- De I-categorie omvatte voorheen combinaties van AB en micro-organismen waarbij de kans op therapeutisch succes niet te voorspellen was:
    - Dat een AB bij een uitslag in de I-categorie in de praktijk vaak vermeden werd, valt wel te begrijpen.
    - De uitslag werd beschouwd als 'gevoeligheid in dit geval onduidelijk'.
- EUCAST heeft met ingang van 2019 de definitie van I veranderd naar 'gevoelig bij verhoogde blootstelling'.
- De nieuwe I biedt, zoals de naam zegt, altijd een reële behandeloptie zolang men het AB hoger doseert dan de standaarddosis.
- Momenteel zitten microbiologische laboratoria in een overgangsfase om deze nieuwe I te implementeren.

De oude I: 'intermediair gevoelig'

- De oude definitie bevatte combinaties van AB en micro-organismen waarbij er sprake was van een onzeker therapeutisch effect, maar de onderliggende argumenten om het therapeutisch effect onzeker te noemen waren divers.
- De I betekende meestal dat het AB wel gebruikt kon worden, zolang men maar hoger doseerde dan de standaarddosis:
    - Bedoeling was om te voorkomen dat het micro-organisme resistentie zou ontwikkelen.
    - Bedoeling was ook om een voldoende hoge concentratie op de plek van infectie te bereiken als het middel daar van nature minder goed doordringt.
    - Kon ook betekenen dat de farmaceut en ontwikkelaars van antibioticabeleid over de klinische effectiviteit onzeker waren, want in het verleden waren de eisen die bij de introductie van een nieuw AB minder streng dan nu.

- Ten slotte kon de I betekenen dat het labo onzeker was over de uitslag door technische variatie in de meetmethode.
- Welk onderliggend argument een rol speelde was niet af te leiden uit de rapportage van I en dat gaf als logisch gevolg dat AB waarvoor de gevoeligheid gerapporteerd werd als I vermeden werden in de praktijk.

De nieuwe I: 'gevoelig bij verhoogde blootstelling'

- De nieuwe definitie bevat enkel nog combinaties van micro-organismen en AB waarbij de kans op therapeutisch succes hoog is zolang men adequaat, d.w.z. hoger, doseert:
  - Uit de definitie van I zijn de componenten 'onzekerheid over klinische effectiviteit' en 'meetonzekerheid in het laboratorium' verwijderd.
  - Ze zijn vanaf nu de verantwoordelijkheid van het microbiologisch laboratorium.
- De nieuwe I is transparant geworden door onder de nieuwe I enkel nog behandelopties op te nemen met een hoge kans op succes:
  - Over de reden waarom een uitslag I is bestaat er geen onduidelijkheid meer.
  - De aanvragende arts weet onder welke voorwaarden gebruik van het betreffende AB aangewezen is.
- Dat is heel duidelijk bij de nieuwe I:
  - Het micro-organisme is gevoelig bij verhoogde blootstelling aan dit AB.
  - Ziet de aanvrager deze uitslag op het antibiogram, dan kan hij of zij ervan uitgaan dat dit, microbiologisch gezien, bij adequate dosering, een goede behandeloptie is.
- Men kan de verhoogde doseringen, die bij de I-categorie nodig zijn, vinden in het landelijke SWAB-ID-antibioticaboekje.
- Ze staan mogelijk ook in het lokale antibioticaboekje als het microbiologisch laboratorium al op de nieuwe definitie van I overgestapt is.

Bepaling van de gevoeligheid in het laboratorium

- Zoals gezegd wordt de gevoeligheid in het antibiogram kwalitatief gerapporteerd in 3 categorieën:
  - Er gebeurt dus een indeling naar de kans op therapeutisch succes. S (= gevoelig), I (= volgens de nieuwe definitie gevoelig bij verhoogde blootstelling) en R (= resistent).
  - De mate van gevoeligheid ligt in werkelijkheid op een continue schaal en deze wordt kwantitatief bepaald.
- In de praktijk wordt vaak gebruik gemaakt van semi-geautomatiseerde systemen om de gevoeligheid te bepalen, al is microdilutie de gouden standaard voor de meeste AB:
  - In het laboratorium bepaalt men bij deze methode visueel wat de laagste concentratie is van een reeks antibioticaverdunningen waarbij er geen groei meer optreedt van het betreffende micro-organisme.
  - Men noemt deze laagste concentratie de minimaal inhiberende concentratie (MIC), uitgedrukt in mg/l.
  - Hoe hoger de MIC binnen een bacteriesoort, hoe resistenter het micro-organisme.
- Deze resistentie kan verworven zijn:
  - Kan bvb. door een mutatie of een combinatie van meerdere mutaties die de binding van een AB beïnvloeden.
  - Kan door effluxpompen die een AB actief ut de cel werken.

- Kan ook door enzymen die het AB afbreken.
- Micro-organismen kunnen ook van zichzelf, los van verworven resistentie, intrinsiek een hoge MIC hebben voor bepaalde AB, zoals Pseudomonas aerigunosa.

Klinische breekpunten voor de indeling in S, I en R

- De gevoeligheid in het antibiogram wordt na bepaling van de MIC gecategoriseerd weergegeven:
  - Dat gebeurt op basis van klinische breekpunten onder de vorm van S, I of R.
  - Men noemt deze breekpunten bewust klinisch omdat ze zo zijn vastgesteld dat ze het therapeutisch succes bij de patiënt voorspellen.
- Er is veel informatie nodig om een klinisch breekpunt vast te stellen:
  - Er moet eerst bekend zijn of de gevoeligheid van het te testen micro-organisme afwijkt van de gebruikelijke gevoeligheid van die soort en daarvoor zijn gegevens nodig over de natuurlijke variatie in de gevoeligheid van dat specifieke micro-organisme.
  - Op basis van klinische en preklinische studies moet ten tweede bekend zijn wat de minimale blootstelling aan een AB is om het micro-organisme te remmen of te doden.
  - Er is tenslotte kennis nodig over de farmacokinetiek van het AB om de vraag te beantwoorden of met de standaarddosering de tot doel gestelde concentratie te bereiken is op de plaats van de infectie.
- Uiteindelijk stelt men op basis van al deze informatie per combinatie van AB en micro-organisme een klinisch breekpunt vast:
  - Dit geeft aan bij welke gevoeligheid en bij welke dosering de kans op therapeutisch succes hoog is.
  - Breekpunten hangen dus af van het micro-organisme, het AB, de dosering en soms van het ziektebeeld.
  - Voorbeeld is wanneer de infectie zich op een plaats voordoet waar een AB van nature minder goed doordringt.

Implicaties voor de behandeling

- De behandelaar kan voor micro-organismen met mogelijk verworven resistentiemechanismen afhankelijk van de gemeten MIC een S, I of R terugvinden op het antibiogram:
  - Is er voor micro-organismen sprake van intrinsiek verminderde gevoeligheid voor een AB, dan werd er voorheen vaak aangenomen dat de behandelaar wist dat er in dat geval hoger gedoseerd moest worden.
  - Voor dit type micro-organismen, waarbij een hogere dosis van toepassing is, zijn de breekpunten vanaf nu zo aangepast dat de aanvrager op zijn best een I op het rapport kan terugvinden (‘gevoelig bij verhoogde blootstelling’), en geen S meer.
  - De behandelaar wordt op deze manier actief geïnformeerd dat een hogere dosis nodig is en dat de kans op therapeutisch succes hierbij hoog is.
- Wordt het AB van eerste keus in het antibiogram gerapporteerd met een I, dan kan het veilig gegeven worden en hoeft de patiënt niet op een AB met een breder spectrum over te gaan:
  - Laatst genoemde aanpak zou zelfs onwenselijk zijn, omdat dat niet effectiever is maar wel onnodig meer soorten bacteriën aanpakt.
  - Dit leidt immers tot selectie van steeds resistentere microbiële

flora bij de patiënt en finaal ook in de algemene bevolking.

- Daarom is het essentieel dat microbiologische laboratoria helder communiceren over het moment waarop zij de aanpassing in de rapportage van I doorvoeren.
- Actieve bijscholing in de microbiologische diagnostiek is een must voor behandelende artsen om hen bekend te maken met de nieuwe I en onnodig gebruik van breedspectrumantibiotica te voorkomen.

Laboratoria moeten verantwoord omgaan met meetonzekerheid

- Er komen veel factoren kijken bij microdilutie of afgeleide technieken:
  - Deze zijn onderhevig aan variabiliteit.
  - Kan gaan om de groeisnelheid van het micro-organisme, de duur van de incubatie, het inoculum, de gebruikte kweekmedia en de temperatuur.
- Streven van de microbiologische laboratoria is om deze factoren zoveel mogelijk te standaardiseren.
- De MIC is desondanks geen vast getal, maar een waarde die kan variëren als de meting zou herhaald worden:
  - Dat is geen probleem bij zeer gevoelige of zeer resistente micro-organismen.
  - Bij MIC's die dichter bij de grens van breekpunten liggen wordt dat lastiger.
- MIC's werden in de oude definitie van I vaak als 'intermediair' gerapporteerd
- Er is tegenwoordig beter bekend waar de meetonzekerheid ligt:
  - Voor microbiologische laboratoria is er bij de invoering van de nieuwe I de parameter 'gebied van onzekerheid' geïntroduceerd.
  - In de internationale literatuur noemt men dit 'area of technical uncertainty' (ATU).
- De ATU is niet voor de aanvragende arts bedoeld , maar gaat om een waarschuwingssysteem dat aangeeft binnen welke grenswaarden het microbiologisch laboratorium kritisch moet nadenken hoe het de uitslag rapporteert:
  - Men kan zo kiezen om bij een MIC die binnen de ATU ligt een ander type confirmatietest in te zetten, zodat men met meer zekerheid een uitspraak kan doen of een uitslag S, I of R is.
  - Nog een alternatief is dat het laboratorium besluit om de uitslag R te rapporteren bij meetonzekerheid, mits er voldoende alternatieven beschikbaar zijn en de uitslag ook geen nadelige consequenties heeft in het kader van 'antimicrobial stewardship'.
  - In uitzonderlijke gevallen kan tenslotte een uitslag gerapporteerd worden met de opmerking dat er sprake is van een onzekere laboratoriumuitslag.
- Men gebruikt hiervoor dan niet meer de letter I, zodat de behandelaar het ontbrekende argument begrijpt en de definitie van de nieuwe I eenduidig blijft, namelijk gevoelig bij verhoogde blootstelling.
- Laboratoria kunnen de omgang met de ATU's individueel bepalen, maar een meer eenduidige werkwijze in de omgang met ATU's zal de vergelijkbaarheid van onderzoeksresultaten tussen laboratoria en de uitwisselbaarheid van uitslagen ten goede komen.

Besluit

- De betekenis van de categorie I verandert in het antibiogram dus landelijk van 'intermediair gevoelig' naar 'gevoelig bij verhoogde blootstelling':

- Het AB biedt dus voortaan bij adequate – t.t.z. verhoogde – dosering met de nieuwe I altijd een reële behandeloptie.
- Men kan in het landelijke SWAB-ID-antibioticaboekje terugvinden welke verhoging van de dosering men moet toepassen bij de uitslag.

- Niet alle microbiologische laboratoria zullen omwille van de grootschalige implementatie de nieuwe I gelijktijdig invoeren en de wijze waarop kan ook in detail verschillen.
- Men wil gaan behandelen met een AB waarvoor het micro-organisme 'gevoelig bij verhoogde blootstelling' is, maar men twijfelt eraan of het medisch microbiologisch laboratorium de nieuwe definitie van I doorgevoerd heeft, of men twijfelt over de juiste dosering voor de behandeling, dan is overleg met de arts-microbioloog of het antibioticateam aangewezen.

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DALENDE OESTROGEENSPIEGEL TIJDENS DE OVERGANG BIJ VROUWEN EN INVLOED OP NYCTURIE

Nycturie is volgens de definitie van de International Continence Society 'het ontwaken om te urineren gedurende de slaap' en vormt een hinderlijk probleem met een grote impact op de kwaliteit van leven.

Enkele cijfers

- Er is een toename van de prevalentie met de leeftijd, zowel bij mannen als bij vrouwen:
  - Men ziet bij vrouwen echter perimenopauzaal een scherpe stijging in de prevalentie, van 16% naar 30% postmenopauzaal.
  - Die toename verloopt bij mannen echter geleidelijker.
- De meeste mensen ervaren twee of meer keren plassen 's nachts als hinderlijk:
  - Urogenitale klachten ziet men bij bijna 90% van de postmenopauzale vrouwen.
  - Naast vaginale droogte is nycturie met 77% de meest voorkomende klacht.
  - Toch is er maar een klein deel van deze vrouwen die hulp zoekt.
- Vrouwen zien nycturie waarschijnlijk als een normaal verouderingsverschijnsel of ze gaan ervan uit dat er geen effectieve behandeling voorhanden is.
- Er is bij nycturie ook een toegenomen risico op morbiditeit:
  - Nycturie geeft op oudere leeftijd o.a. een 2 keer zo hoog risico op vallen en heupfracturen.
  - Heeft ook een negatieve invloed op de normale slaapcyclus, waardoor de kans op psychische symptomen, type prikkelbaarheid en depressie, groter is.
- Bij valneigingen, psychische klachten en slaapstoornissen zouden huisartsen vaker kunnen vragennaar nycturie.

Pathofysiologie

- De pathogenese van nycturie is complex, met als belangrijkste oorzaken (1) een afgenomen (nachtelijke) blaascapaciteit, (2) nachtelijke polyurie en (3) globale polyurie.
- Bij een significant deel van de ouder wordende vrouwen is er echter een gecombineerde vorm van nycturie: hierbij spelen zowel nachtelijke polyurie als afgenomen blaascapaciteit een rol.
- Slaapverstorende factoren, zoals het restless-legs syndrome (RLS), de periodic limb movement disorder (PLMD), het obstructieveslaapapneusyndroom (OSAS) of nachtzweten/opvliegers kunnen bovendien aanleiding geven tot frequent ontwaken, waardoor de patiënt vaker een prikkel voelt om te plassen (convenience voidings).

Anamnese en aanvullend onderzoek

- Doel hiervan is om onderscheid te maken tussen de 3 genoemde vormen van nycturie.
- Bij het maken van het onderscheid kan bestaande comorbiditeit, zoals hartfalen, nierfalen/nefrotisch syndroom, veneuze insufficiëntie met oedeem en DM of medicatiegebruik helpen bij het maken van het onderscheid.
- Het belangrijkste diagnostische instrument wordt echter gevormd door het mictiedagboek: dit maakt immers duidelijk wanneer er sprake is van een afgenomen blaascapaciteit, een

nachtelijke polyurie of een globale polyurie.
- Vervolgens geeft dit onderscheid in 3 oorzaken, al dan niet in combinatie met klachten door daling van de oestrogeenspiegel, richting aan de adviezen en behandeling bij vrouwen.

Algemene behandeling

- Een eerste vereiste zijn adviezen over een gezonde leefstijl, en dat ongeacht de oorzaak:
    - Voldoende, maar niet overmatig drinken (1,5-2 liter per dag).
    - Verminderen van de zoutconsumptie en blaasprikkelende vloeistoffen (cafeïne en/of alcohol).
    - Vermijd inname van vocht 2 uur voor bedtijd.
    - Ledig de blaas voor het slapengaan.
- Wanneer anamnese en mictiedagboek op een afgenomen (nachtelijke) blaascapaciteit wijzen, adviseert men de patiënt om voldoende te drinken en blaasprikkelende vloeistoffen te vermijden:
    - De belangrijkste stap in de behandeling is blaastraining.
    - Men is best terughoudend met het voorschrijven van anticholinergica, niet alleen omdat het effect hiervan t.o.v. een placebo gering is, maar vooral omdat de kans op bijwerkingen bij ouderen groot is.
    - 43-83% van de patiënten staakt binnen de 30 dagen de behandeling.
- Er zijn aanwijzingen voor een globale polyurie, zoals polydipsie:
    - Hier luidt het advies om de vochtinname te beperken.
    - Hangt het ontstaan van polydipsie/polyurie samen met DM, dan zal de glucose-instelling moeten geoptimaliseerd worden.
- Diagnose en behandeling van nachtelijke polyurie zijn ingewikkeld:
    - Men kan theoretisch onderscheid maken tussen verhoogde water- en verhoogde natriumuitscheiding.
    - Diagnosestelling en behandeling ervan zijn niet voor de eerste lijn geschikt.
    - Omwille van een aanzienlijke kans op (ernstige) hyponatriëmie , vooral bij vrouwen, valt een eventuele proefbehandeling met desmopressine af te raden.
    - Advies van de huidige NHG-Standaard Hartfalen is om een diureticum voor te schrijven als er duidelijke aanwijzingen voor hartfalen zijn.

Peri- en postmenopauzale veranderingen door dalende (endogene) oestrogeenspiegels

- Deze daling tijdens de overgang vermindert de activiteit van oestrogeenreceptoren in verschillende eindorganen en draagt bij aan het ontstaan van nycturie.
- Receptoren in de blaas, vagina en urethra:
    - Er is een verdunning van het epitheliale en gladde spierweefsel van de blaas en een afname van de doorbloeding van de vagina en de blaas.
    - Resultaat van deze veranderingen is een naar schatting 50% vermindering van de functionele blaascapaciteit.
    - Hoogstwaarschijnlijk is dit mechanisme 1 van de oorzaken van het overactieve blaassyndroom bij oudere vrouwen en gekenmerkt door urgency, frequency en nycturie.

- Receptoren in de mondmucosa en speekselklieren:
    - Door lagere activiteit van oestrogenen ontstaat er een droge mond en dorst.
    - Dit kan leiden tot een toename van de globale 24-uurs- en avondinname van vocht.
    - Op zijn beurt leidt dit tot een toename van (nachtelijke) diurese.
- Receptoren in de hypofyse en hypothalamus:
    - Bij minder oestrogeenactiviteit krijg je minder secretie van antidiuretisch hormoon (ADH).
    - Dit is een van de belangrijkste hormonen in de waterhuishouding.
    - In de nachtelijke uren stijgt ADH normaliter en neemt de nachtelijke diurese af.
    - Door de verlaging van ADH krijgt men dus omgekeerd nachtelijke polyurie.
- Daarnaast heeft de daling van oestrogenen ook een direct effect op de nieren, omdat deze ze minder gevoelig maakt voor ADH.
- Door nachtelijk zweten en nachtelijke opvliegers leidt een vermindering van oestrogenen ook tot slaapproblemen en frequent ontwaken, waardoor de patiënt vaker een prikkel kan voelen om te gaan plassen.

Mogelijke aanpak van deze problemen

- In eerste instantie gelden bij overgangsgerelateerde klachten, zoals opvliegers, de volgende leefstijladviezen:
    - Verlaag de slaapkamertemperatuur en zorg voor een goede ventilatie.
    - Zorg voor kleding en bedlinnen in laagjes.
    - Vermijd aanwijsbare triggers voor opvliegers, zoals alcohol en pittig eten.
- De afname van de oestrogenen beïnvloedt dus de klacht van nycturie, maar toch is er weinig onderzoek uitgevoerd naar het effect van hormoonsuppletie:
    - Over de rol van hormonale substitutietherapie (HST) bij de behandeling van nycturie bestaat er nauwelijks tot geen bewijs.
    - Advies van de International Consultation on Incontinence Research Society (ICIRC) luidt op basis van expertconsensus als volgt: schrijf voor nycturie in de overgang alleen HST in combinatie met leefstijladviezen voor als er ook nachtelijke opvliegers zijn.
    - De effectiviteit van oestrogenen is ook voor lokaal vaginaal gebruik bij enkel de klacht nycturie beperkt.
- Uit een systematische review over de effectiviteit van vaginaal gebruik van oestrogenen volgt de conclusie dat de nachtelijke mictiefrequentie slechts in 3 van de 5 onderzoeken daalt in vergelijking met placebo.
- Men kan volgens de richtlijn van de ICIRC vaginaal gebruik van oestrogenen ter ondersteuning van het urogenitale stelsel bij nycturie overwegen als er ook andere vaginale klachten zijn, zoals vaginale droogte.

Besluit

- Mits een goede anamnese en kennis van het mictiedagboek zijn de 3 belangrijkste oorzaken van nycturie op te sporen.

- Vraag ook bij slaapstoornissen, psychische klachten en valneigingen (bij ouderen) naar nycturie.
    - Men kan, afhankelijk van de oorzaken, een gericht advies en/of behandeling geven.
    - Bij elk van die oorzaken kan bij peri- en postmenopauzale vrouwen een daling van de oestrogeenspiegel ook een rol spelen.

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Met dank aan dr. Willy Storms

Bronnen

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MCH WEBSITE

Op onze website www.mchinfo.be kan u nog veel meer informatie vinden.

REACTIES

Opmerkingen, ideeën of vragen zijn steeds welkom bij Bianca Thys, communicatieverantwoordelijke: focus@mchinfo.be

UITSCHRIJVEN

Indien u wilt dat we uw naam van onze verzendlijst verwijderen, stuur dan een mail naar: focus@mchinfo.be

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