education

FROM THE JOURNALS Edited highlights of Richard Lehman's blog on http://bmj.co/Lehman

Cardiac arrest during sport

Some people enjoy playing physical games, and lots of people enjoy watching them. It was the great Michael O'Donnell who taught me the distinction between games—fun, voluntary, human—versus "sport," with its connotations of obsessive competitiveness and commercial capture. I guess it's hard to have the first without it turning into the other. Here's a Canadian observational study called "Sudden cardiac arrest during participation in competitive sports," and it finds that many more people die suddenly during games ("non-competitive sports": 58 deaths per 18.5 person-years of observation) than during competitive sport (16 deaths). "Just three cases of sudden cardiac arrest that occurred during participation in competitive sports were determined to have been potentially identifiable if the athletes had undergone preparticipation screening." I will leave it to sportier people to mull over these data and their implications for screening.

N Engl J Med doi:10.1056/NEJMoa1615710

Diuretics in heart failure

Now, if you asked an ordinary member of the public what these sports people (12 men, 3 women) died of, I bet you about a half would say "heart failure." Only among doctors does "acute heart failure" mean anything other than sudden death. For us it is synonymous with pulmonary oedema of rapid onset, which often responds quickly to the administration of an intravenous loop diuretic. So far, so satisfying. But, while diuretics have an essential role in management of heart failure, every clinician (in primary care, especially) knows that responses vary and tailoring of treatment can be very difficult. Long term treatment with loop diuretics induces profound renal changes, which can often result in diuretic resistance. Here is a really excellent review that should be read by everyone who manages heart failure. Moreover, it is lavishly illustrated with those pink, purple, and green illustrations of loops of Henle and basement membrane ion exchange blobby things which keep us slavering for the next sheeny paper issue of *NEJM*.

N Engl J Med 10.1056/NEJMra1703100

When to lower blood pressure, again

"In this systematic review and meta-analysis, including 74 trials and more than 300 000 patients, treatment to lower blood pressure was associated with a reduced risk for death and cardiovascular disease if baseline systolic blood pressure was 140 mm Hg or above. Below 140 mm Hg, the treatment effect was neutral in primary preventive trials, but with possible benefit on non-fatal cardiovascular events in trials of patients with coronary heart disease."

This comes in the week that the American Heart Association published its new hypertension guideline, based on its own systematic review. That sets the threshold at 130 mm Hg and at last introduces the idea of an assessment of total cardiovascular risk. But it reclassifies about half the population as "hypertensive." Here lies a glimmer of hope. When this level of absurdity is reached, people might start questioning the notion of "hypertension" altogether, in favour of seeing how their own blood pressure affects their personal risk. They might want to use an interactive risk calculator, so they can get some idea of the likely benefit to themselves as individuals if they opt for particular lifelong treatments. Our job is to provide them with easily updated, road tested tools and let them choose for themselves, without bothering them with our arbitrary, population based thresholds. I hope I live to see it happen.

JAMA Intern Med doi:10.1001/jamainternmed.2017.6015

Thrombectomy for occlusive stroke, again

The first revolution in stroke management was thrombolysis: clot retrieval (thrombectomy) is the second, and it is reshaping the provision of stroke services. For both procedures, time means brain. But the DAWN trial shows that, even after six hours, some patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery might benefit from thrombectomy. These are the ones with a mismatch between the severity of the clinical deficit and the infarct volume. I won't go into detail—I am just conveying the fact that acute stroke care is still in a state of progress.

N Engl J Med doi:10.1056/NEJMoa1706442

Non-hormonal treatments for menopausal symptoms

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This is an edited version; the full version is on bmj.com

Menopause is a normal event, and most women do not seek medical intervention. Of those who do, some will require only information and advice, but around 25% have problematic symptoms that may need treatment. Vasomotor symptoms are the main reason for seeking treatment. Hormone replacement therapy is effective for vasomotor symptoms, but for some it is unsuitable (due to preference or contraindications) and non-hormonal treatments can be considered.

This update provides an overview of the evidence supporting non-hormonal treatments for vasomotor and vaginal symptoms, and guidance on managing these symptoms in clinical practice.

CPD READING
0.5 HOURS

What are menopausal symptoms?

The menopause is the final menstrual period. The "perimenopause" or "menopause transition" is the time from the onset of menstrual cycle changes until one year after the final menstrual period.[1]

Changes in vaginal bleeding patterns and vasomotor symptoms characterise the menopause transition, but the overall experience is highly variable and may be influenced by psychological, social, and cultural factors.[2] Common symptoms include hot flushes and night sweats (vasomotor symptoms) and genital symptoms (vaginal dryness, dyspareunia), which may be accompanied by mood and sleep disturbance.[3]

WHAT YOU NEED TO KNOW

- Menopause is a normal event, but around 25% of women have problematic vasomotor symptoms (hot flushes and night sweats) that impair quality of life and might require treatment
- Systemic hormone replacement therapy (HRT) is currently the most effective treatment for vasomotor symptoms and may also improve vaginal dryness, sleep, and quality of life
- For those wishing to avoid HRT, there are non-pharmacological and non-hormonal pharmacological treatments for vasomotor symptoms
- Most non-hormonal treatments act quickly, so if there is no improvement after 2-4 weeks consider a different approach
- Management of menopausal symptoms should be individualised and address patient aims and preferences for treatment. Therapies should target the symptoms that most affect function and quality of life

Who is affected?

Vasomotor symptoms affect about 80% of women, with around 25% reporting problematic symptoms that affect quality of life.[6-8] Vasomotor symptoms usually occur daily and may continue for 4-10 years[9] with a peak in the year around the final menstrual period.[10 11] Vaginal symptoms (dryness and/or dyspareunia) affect around a third of women and tend to persist until older age (age 80 years) or may appear some years after the menopause.[12] Around a third of women experience sleep disturbance during the menopause transition,[13] and an estimated 10% have depressive symptoms, which tend to resolve in the postmenopause and may be associated with psychosocial factors.[14]

Why are non-hormonal treatments needed?

Hormone replacement therapy (HRT or HT) is the most effective treatment for menopausal symptoms but is contraindicated for some women and avoided by others. Vasomotor symptoms are common in breast cancer patients and may be more severe and persistent than in the general population.[19] Systemic HRT is avoided after breast cancer, and non-hormonal treatments may be needed. Most women experience a resurgence of vasomotor symptoms when HRT is discontinued,[20] which may require treatment with non-hormonal approaches. Differences in study populations, variations in outcome measures, a paucity of head-to-head comparisons between non-hormonal and hormonal treatments and conflicting advice in guidelines about the efficacy of non-hormonal treatments has complicated clinical management. The figure provides a suggested approach to using non-hormonal treatments for a patient with problematic menopausal symptoms.

Non-pharmacological treatments for vasomotor symptoms

Cognitive behavioural therapy

Cognitive behavioural therapy (CBT) effectively reduced the impact (problem rating) of vasomotor symptoms in women with and without a history of breast cancer, by an average of 50% after 8 hours of group CBT (weekly group sessions over 4-6 weeks)

with benefits maintained at six months (see table, bmj.com).[15-39] CBT also reduced subjective frequency of night sweats by an average of 39% and reduced objectively measured vasomotor symptoms (sternal skin conductance monitoring) in well women,[40] but not in breast cancer patients.[16] This may reflect differences in the nature of menopausal symptoms in breast cancer patients.[41] The North American Menopause Society (NAMS) guidelines recommend CBT for the treatment of vasomotor symptoms.[17]

A systematic review concluded that exercise does not improve vasomotor symptoms or sleep

Hypnosis

The NAMS guideline recommends hypnosis for the treatment of vasomotor symptoms,[17] based on randomised controlled trials including women with [25] and without a history of breast cancer[26] demonstrating a statistically significant reduction in the frequency of subjective and objective vasomotor symptoms (measured by sternal skin conductance monitoring) and subjective severity after five weekly sessions (each an hour long) of hypnosis plus practice at home.

Mindfulness and relaxation

Current evidence does not support the efficacy of mindfulness based stress reduction (MBSR) or relaxation for vasomotor symptoms. One randomised controlled trial of 110 women found no statistically significant improvement in vasomotor symptoms (compared with a wait list control) after 20 hours of MBSR (P=0.116),[42] and a systematic review of four randomised controlled trials (including 261 women) of relaxation techniques for vasomotor symptoms concluded that the quality of published studies was generally poor and that there was insufficient evidence to recommend these treatments.[43]

Lifestyle changes

Some women can identify specific triggers for their vasomotor symptoms. Avoiding these and facilitating cooling down (such as by dressing in layers) may help some women, but there is no high quality evidence supporting this.[17] Paced breathing was previously recommended but has been found to be ineffective (compared with a control of rapid shallow breathing).[44] The efficacy of cooling devices, such as pads, gels, and collars has not yet been adequately evaluated but studies are in progress (clinicaltrials.gov. NCT02795741).

Diet and supplements

A systematic review of randomised controlled trials of plant based therapies concluded that dietary or supplementary phytoestrogens modestly improve hot flushes (average reduction in the number of hot flushes of 1.3 per day) and vaginal dryness but do not improve night sweats. While the overall quality of evidence for these therapies is poor,[45] current evidence from randomised controlled trials does not support specific diet regimens such as plant based diets or diets rich in fish for the management of vasomotor symptoms.

There is limited evidence from randomised controlled trials that isoflavones (soy) or black cohosh may relieve vasomotor symptoms.[46] However, a 2016 systematic review and a meta-analysis concluded that there is currently insufficient evidence to support the use of black cohosh for vasomotor symptoms.[45] Another systematic review of black cohosh for vasomotor symptoms reached a similar conclusion.[47] More recently, a parallel, double blind, randomised controlled trial of 63 women showed that a combination of probiotic and red clover isoflavone was superior to placebo and reduced the frequency of vasomotor symptoms by 4.3 hot flushes per day on average compared with <1 per day with placebo (P<0.01, 95% CI −6.8 to −2.3).[48] NICE guidelines on management of early breast cancer recommend avoiding black cohosh and isoflavones in breast cancer patients.[38]

Vitamins

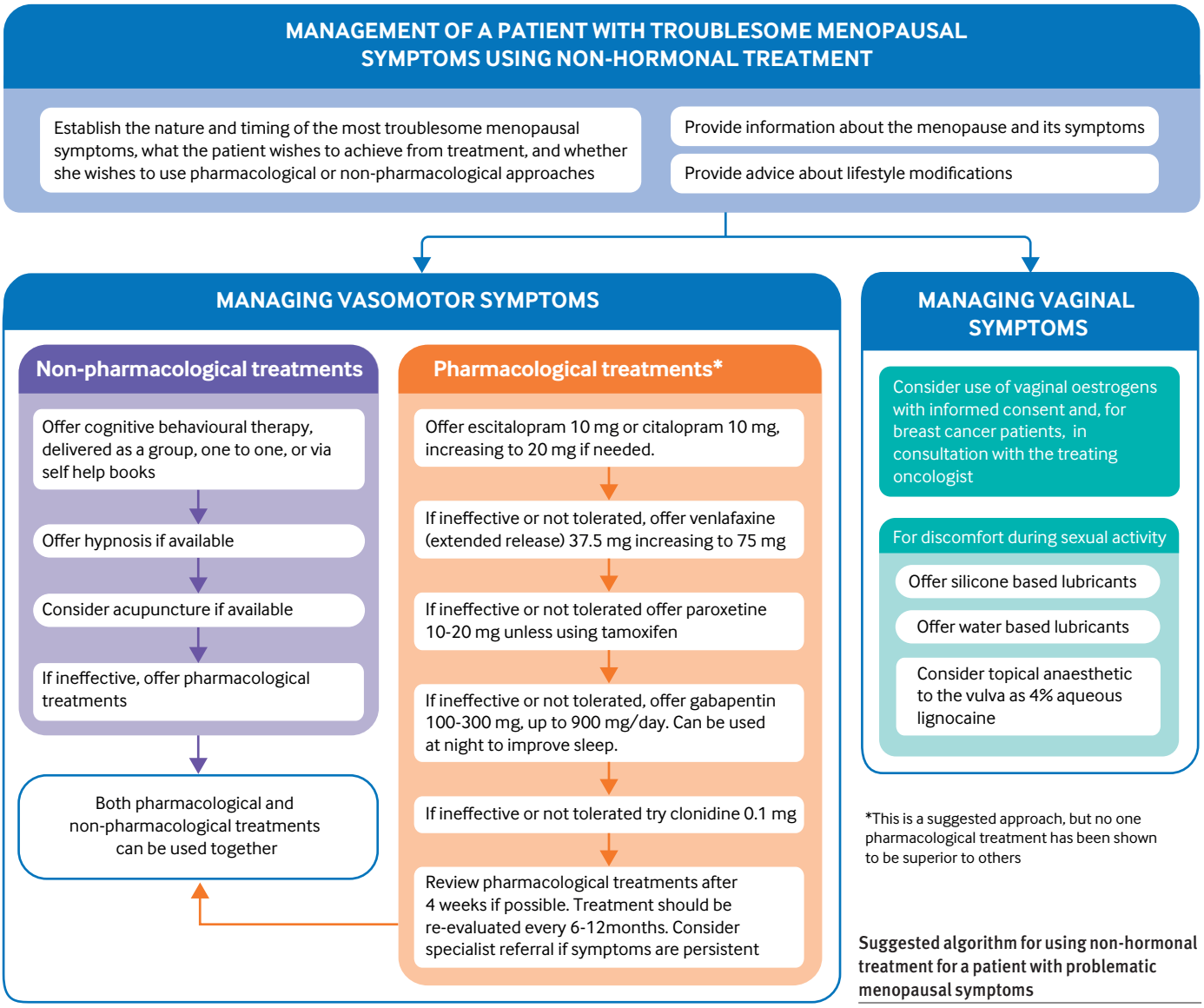
One randomised, placebo controlled trial of vitamin E (800 IU/day) in 105 breast cancer survivors produced a small reduction in frequency in vasomotor symptoms of less than one hot flush per day.[49] A trial of gabapentin versus vitamin E in 115 breast cancer survivors found that vitamin E was less effective than gabapentin for vasomotor symptoms (57% reduction in hot flush frequency with gabapentin versus 10% with vitamin E).[50]

Exercise

A systematic review of five randomised controlled trials including 733 women concluded that exercise does not improve vasomotor symptoms or sleep, although it is likely to confer other health benefits.[45 51] Comparing exercise with usual activity (three studies, 454 women), there was no difference between groups in the frequency or intensity of vasomotor symptoms (standardised mean difference −0.10, 95% CI −0.33 to 0.13, I^2=30%), but the quality of evidence was considered to be low.

Yoga

Current evidence does not support the efficacy of yoga for improving vasomotor symptoms. A randomised trial of yoga, 12 weekly 90-minute classes with daily home practice, (n=107) versus aerobic exercise training three times a week for 12 weeks (n=106) or usual activity



Suggested algorithm for using non-hormonal treatment for a patient with problematic menopausal symptoms

(n=142) in women with vasomotor symptoms reported that neither yoga or exercise reduced vasomotor symptoms, but both yoga and exercise improved sleep quality,[52] and exercise also improved mood.[53]

Weight loss

Longitudinal studies show that higher body mass index is a risk factor for vasomotor symptoms (odds ratio 1.03).[54] The NAMS guideline advises that weight loss in overweight women may be beneficial for menopausal symptoms but this is not yet supported by high quality evidence.[17]

Stellate ganglion block

Injecting local anaesthetic into the sympathetic nerve fibres of the neck (the stellate ganglion) disrupts neural temperature regulation. This is an invasive and costly procedure, and the NAMS guidelines state that more evidence is needed from ongoing trials before stellate ganglion block can be recommended for vasomotor symptoms.[17]

Complementary and alternative treatments for vasomotor symptoms

The most popular complementary and alternative medicines (CAMs) are herbal medicine, followed by soy or phytoestrogens, evening primrose oil, relaxation, and yoga.[55] Current evidence does not support the use of CAMs for vasomotor symptoms. NICE recommends that clinicians should explain that many CAMs are available, that their safety is uncertain, and that interactions with other medicines have been reported.[46] If patients choose herbal treatments they should be advised to look for the MHRA "traditional herbal remedy" stamp validating strength and quality.[57]

Non-hormonal pharmacological treatments for vasomotor symptoms

Developing novel targeted treatments for vasomotor symptoms has been limited by poor understanding of the underlying mechanisms. Pharmacological treatments demonstrated in randomised placebo controlled trials to improve vasomotor symptoms

EDUCATION INTO PRACTICE

- How can you incorporate a decision support tool for non-hormonal management of vasomotor symptoms into treatment discussions (such as that developed by NAMS[86])?
- How can you better communicate the information about common menopausal symptoms and evidence based treatment options to women?

include selected serotonin selective reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), gabapentin, and clonidine.[34 35]

Serotonin selective reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors

International guidelines[17-61] and systematic reviews of randomised controlled trials[21-35] recommend selected SSRI and SNRI for the non-hormonal management of vasomotor symptoms. However, NICE recommends that pharmacological non-hormonal treatments should not be offered as first line treatments for vasomotor symptoms alone.[46] Breast cancer patients commonly experience vasomotor symptoms. Those taking tamoxifen as endocrine therapy, or high-risk women taking tamoxifen to reduce their breast cancer risk should avoid the SSRIs fluoxetine and paroxetine since these impair conversion of tamoxifen to its active metabolite, potentially diminishing its efficacy.[34]

A randomised trial comparing the SNRI venlafaxine (extended release, 75 mg/day) with 0.5 mg/day oral 17β oestradiol found that both treatments were associated with a statistically significant reduction in the frequency of vasomotor symptoms of around 50% after eight weeks of use.[63] Oestradiol improved menopause-related quality of life (as measured by the MENQOL[64]) more than venlafaxine.[65] Neither treatment affected sexual function over an eight week treatment period,[66] and both significantly improved sleep quality compared with placebo.[63-67] Oestradiol at this dose is effective for at least four years for vasomotor symptoms,[68] but the long term efficacy of venlafaxine is not known.

Gabapentin and pregabalin

Gabapentin is an anticonvulsant also used for neuropathic pain. A systematic review of 13 randomised controlled trials including 1714 women found that gabapentin (300 mg three times per day) reduced the severity and frequency of vasomotor symptoms in breast cancer survivors (table 1).[34] Up to 900 mg/day gabapentin is generally well tolerated, but side effects are dose related and may include somnolence, dizziness, and fatigue.[35 36] A randomised controlled trial in 163 breast cancer survivors found that pregabalin (75 mg twice daily) significantly reduced the frequency and severity of vasomotor symptoms (table 1).[37] Gabapentin and pregabalin are not licensed for the treatment of vasomotor symptoms in the UK.

Clonidine

Clonidine is a centrally active α-2 adrenergic agonist anti-hypertensive. It is the only licensed non-hormonal medicine for vasomotor symptoms in the UK. A double-blind, randomised, placebo controlled trial of clonidine (0.1 mg/day) versus venlafaxine (75 mg/day extended release) versus placebo in 102 breast cancer survivors over 12 weeks showed that both clonidine and venlafaxine were superior to placebo in reducing vasomotor symptoms and, although venlafaxine worked more quickly, clonidine was more effective at 12 weeks.[71] Side effects of clonidine include dizziness, hypotension, headache, constipation, and dry mouth.[23]

Topical treatments for vaginal symptoms of menopause

Topical oestrogen

Vaginal symptoms such as dryness and dyspareunia are common in postmenopausal women and can affect relationships and sexual function. Vaginal (topical) oestrogen is the most effective treatment for symptoms, and systemic absorption is minimal. Vaginal dryness is also common in breast cancer survivors, particularly in women taking aromatase inhibitors.[72] In addition to their negative impact on quality of life, vaginal dryness and discomfort may lead to discontinuation of endocrine therapy for breast cancer, which in turn reduces disease-free survival.[73] Guidelines from the American College of Obstetrics and Gynaecology recommend reserving vaginal oestrogens for intransigent vaginal dryness in breast cancer survivors, discussion with the treating oncologist, and inclusion of the patient in decision making when considering potential risks and benefits.[76]

Vaginal moisturisers

Non-hormonal options for vaginal dryness are limited. Moisturisers are marketed as long term treatments[78] but mainly contain water and there is little evidence that they lead to clinical improvements in symptoms. Moisturisers can cause local irritation,[17] and this may be more marked in preparations where the osmolality and pH differ from normal vaginal secretions.[78] There is insufficient comparative data to recommend one vaginal moisturiser over another.

Vaginal lubricants

Vaginal lubricants can be used during sexual activity to reduce friction. Lubricants may be water based, silicone based, or plant oil based (such as olive oil). One double-blind placebo controlled trial of a pH balanced vaginal gel for vaginal dryness in 86 breast cancer survivors found that the pH balanced gel was more effective than placebo for vaginal dryness and dyspareunia.[79] In 38 breast cancer survivors with discomfort during sexual activity, one randomised crossover trial comparing a silicone based and a water based lubricant found that the silicone based lubricant was more effective in reducing pain and discomfort during intercourse (odds ratio 5.4, 95 % CI 1.3 to 22.1, P=0.02). However, most women (88%) continued to experience clinically significant sexually related distress despite use of either lubricant.[80 81] Vulvar symptoms may also contribute to sexual discomfort. One randomised, placebo controlled, double blind trial of 4% aqueous lidocaine (*v* saline) applied to the vulvar vestibule for 3 minutes before vaginal penetration statistically significantly reduced pain during intercourse in breast cancer survivors with severe dyspareunia.[82]

Competing interests: None declared.

Cite this as: *BMJ* 2017;360:j5101

Find the full version with references at http://dx.doi.org/10.1136/bmj.j5101

Non-antibiotic options for recurrent urinary tract infections in women

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CPD READING
0.5 HOURS

Recurrent urinary tract infection in women is a common problem. There is no universally accepted definition, but most clinicians would classify recurrent UTI as being two episodes of infection in six months, or three episodes in one year.[1] The annual incidence of a single UTI is 30 per 1000 women,[2] with 44% experiencing recurrence within 12 months.[3]

Guidelines from the Scottish Intercollegiate Guidelines Network[4] and the European Association of Urology[1] recommend the use of low dose prophylactic antibiotics for preventive treatment of recurrent UTI. The largest systematic review and meta-analysis of the effect of prophylactic antibiotics on recurrence rates includes 19 randomised controlled trials with data from 1120 women[5] and reports an 85% reduction in the incidence of symptomatic UTI compared with placebo (relative risk 0.15, 95% confidence interval 0.08 to 0.28). This review examined data from girls and women over 14 with a history of at least two episodes of uncomplicated UTI and calculated that the number needed to treat with prophylactic antibiotics to prevent recurrence over a 6-12 month period was 1.85[5] (however, the authors commented that the quality of the included studies was poor).

Prolonged antibiotic use in women has resulted in the emergence of resistant organisms in their urine. A randomised controlled trial of 252 women who had been through menopause showed that, if resistance develops, it is often to multiple antimicrobial agents and not just the primary drug that the patient has been prescribed.[6] This trial, comparing antibiotic prophylaxis against urinary tract infections with an oral *Lactobacillus* preparation, found that, in the antibiotic arm (trimethoprim), resistance to other antibiotic agents such as amoxycillin and co-trimoxazole doubled over a period of one month.[6] Resistant micro-organisms can develop after just a few weeks of treatment. A prospective cohort study involving 136 students who were given trimethoprim for two weeks found resistance to at least four antibiotics in 96% of *Escherichia coli* from faecal isolates.[7] Consequently, other treatment options are of interest.

Emerging potentially efficacious non-antibiotic treatments for prevention of recurrent UTI could minimise the development of antimicrobial resistance in bowel reservoirs but there is a paucity of high level evidence to demonstrate their effectiveness.

Prolonged antibiotic use in women has resulted in the emergence of resistant organisms in their urine

WHAT YOU NEED TO KNOW

- After treating the acute infection, low dose antibiotics given for 6-12 months are the most evidence based preventive measure for recurrent urinary tract infections (UTIs) in women, and are recommended by national and international guidelines as the standard of care
- There is evidence of antimicrobial resistance development with prolonged low dose antibiotics and this has led to the investigation of non-antibiotic alternatives to prevent UTIs
- Evidence for non-antibiotic treatments is variable: vaginal oestrogens, D-mannose, immunotherapy, and methenamine look most promising

What is the evidence for uncertainty?

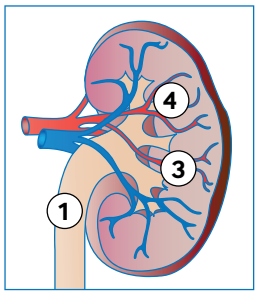
Despite the existence of several up to date Cochrane meta-analyses on the subject of recurrent UTI prevention, uncertainty remains because of the lack of good quality comparative head to head trials. Consequently, precise quantification of the risks and benefits of prolonged non-antibiotic treatments is yet to be established.

Urinary alkalisation

A meta-analysis examining the efficacy of urinary alkalinisation for prevention of recurrent UTI screened 172 randomised controlled trials, all of which failed to meet the inclusion criteria because of poorly defined study populations, interventions, and a lack of comparators (table 1). No recommendations could be made, therefore, for the use of urinary alkalisation.[8] No comment can be made regarding the risks or adverse events of urinary alkalinisation, but recognised side effects include gastrointestinal symptoms such as nausea and flatulence and mild diuresis.

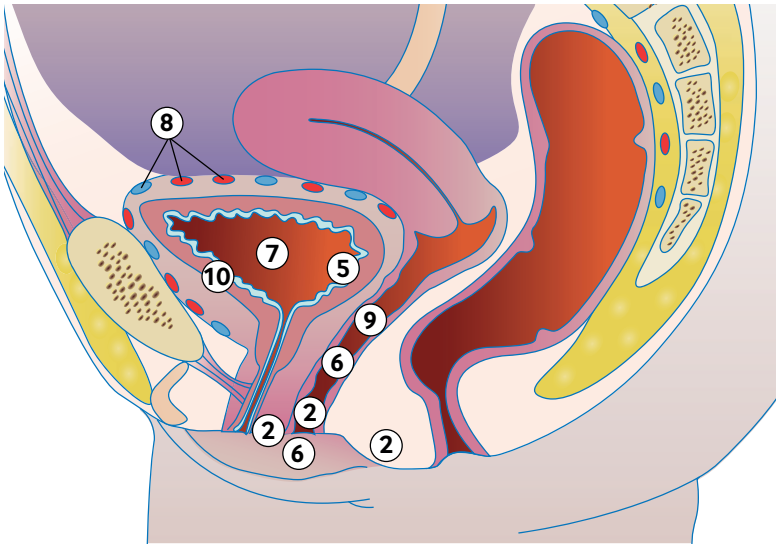
WHAT TO TELL PATIENTS

- Most women with recurrent UTI will have a structurally and functionally normal urinary tract, therefore treatment is based on prevention and reducing infection frequency
- Low dose antibiotics for 6-12 months carry the highest chance of success in reducing the frequency of UTI
- Avoiding the development of antibiotic resistance is best achieved with non-antibiotic measures, but it is unclear how effective these are



Key
Location of action/effect

1 Urinary alkalisation
2 Probiotis
3 Chinese herbal medicine
4 Methenamine hippurate
5 Cranberry
6 Topical oestrogen
7 Intravesical hyaluronic acid
8 Oral immunostimulants
9 Vaginal vaccines
10 D-Mannose



How treatments act on the kidney (top left) and urinary tract

Probiotics

Probiotics in recurrent UTI were the subject of a recent Cochrane systematic review and meta-analysis including nine randomised controlled trials of 735 patients.[9] No statistically significant benefit (relative risk 0.82 *v* placebo [95% confidence interval 0.6 to 1.12]; relative risk 1.12 *v* antibiotics [95% confidence interval 0.95 to 1.33]) was shown for probiotics over placebo or no treatment, but the authors concluded that a benefit cannot be ruled out as the number of patients was small, and the trials had poor methodological reporting because of high reporting and attrition bias. Reported side effects of probiotics included vaginal discharge, genital irritation, and diarrhoea, but these affected only 23 out of 735 women.

Chinese herbal medicine

In a 2015 Cochrane review, meta-analysis of three randomised controlled trials involving 282 women that looked at Chinese herbal medicine compared with antibiotics suggested that the Chinese herbal medicine reduced recurrent UTI rates (relative risk 0.28, 95% confidence interval 0.09 to 0.82), but the authors advised caution because of the small study sizes, the high risk of bias, and the lack of evidence in the premenopausal population. Only two studies reported on adverse events, and neither found any change in liver or kidney function. It was not explained in the review how this was assessed.

Methenamine hippurate

In a 2012 Cochrane review, methenamine hippurate[11] was associated with a reduction in risk of UTI in patients with normal renal tracts (relative risk 0.24, 95% confidence interval 0.07 to 0.89) and was found to be well tolerated. However, only one of the trials—of 30 patients—included in this review looked specifically at people with recurrent UTI, and found that methenamine was associated with a reduction in UTI (relative risk 0.46). Low rates of adverse events were reported across all included studies. Nausea was the most common symptom, and was noted in 12 of 2032 people. Single instances of rash, diarrhoea, sore throat, and bladder "stinging" were also described. Given the demonstrable benefit of methenamine hippurate and its excellent side effect profile, it is one of the most promising non-antibiotic treatments for recurrent UTI, and is currently subject to an ongoing multicentre UK randomised controlled trial.[14]

Cranberry

A Cochrane review in 2008[15] found a reduction in the incidence of recurrent UTI (relative risk 0.65, 95% confidence interval 0.46 to 0.9), but, since the dropout rates for several of these studies was high, there was a high risk of bias. An updated 2012 Cochrane review including an additional 14 studies and 4473 participants (table 1) suggested that cranberry juice was less effective than previously indicated; cranberry products (juice or dietary supplements based on fruit extracts) did not statistically significantly reduce the occurrence of symptomatic UTI overall (relative risk 0.86, 95% confidence interval 0.71 to 1.04) compared with placebo or no treatment. The subgroup analysis for women with recurrent UTIs also showed no difference (relative risk 0.74, 95% confidence interval 0.42 to 1.31). The authors concluded that cranberry juice could not be recommended for the prevention of UTI.

Although adverse events from taking cranberry products, such as gastrointestinal disturbance, were similar to those of placebo/no treatment, many studies reported low compliance and high dropout rates, which were attributed to palatability of the products.

Oral immunostimulants

A meta-analysis in 2009 (four randomised controlled trials, 891 patients) of oral immunostimulants looking at their effectiveness showed a benefit in decreasing recurrent UTI (relative risk 0.61, 95% confidence interval 0.48 to 0.78).[16] However, a later randomised double blind trial (2015) involving 451 women with recurrent uncomplicated UTI found no benefit of oral immunostimulants compared with placebo.[17] Guidelines from the European Association of Urology[1] support their use.

HOW PATIENTS WERE INVOLVED IN THIS ARTICLE

There was no patient involvement from the authors when constructing this article. However, the patient reviewer highlighted the importance of patient reported outcome measures in any future or planned trials in addition to traditional microbiological tests.

WHEN TO INVESTIGATE FURTHER

Most women presenting with recurrent UTI have uncomplicated infections (defined as no structural or functional urinary tract abnormalities).[1] Current international guidelines do not recommend routine investigations of women with recurrent UTI because of their low diagnostic yield.[1] Symptoms such as persistent loin pain, haematuria, or the presence of atypical infection would necessitate referral to secondary care, where further tests (renal tract ultrasound/computed tomography, flexible cystoscopy, and urine flow studies/post-void urine estimation) can be carried out.

EDUCATION INTO PRACTICE

When a patient presents with recurrent UTIs, ask yourself:

- Have I addressed all modifiable risk factors for this patient—eg, adequate fluid intake, diabetic control, oestrogen depletion, and constipation, before recourse to preventive measures?
- Do I need to perform further investigations in this patient, or am I happy that this is an uncomplicated recurrent UTI?
- Have I discussed the potential risks and benefits of the standard treatment of prophylactic antibiotics with the patient? Should we consider the use of a non-antibiotic alternative in the light of the evidence presented?

Topical oestrogen

Topical vaginal oestrogen, when used primarily as a treatment for recurrent UTI, was shown to be beneficial in reducing the incidence of infection in women who have been through menopause in a meta-analysis of five randomised controlled trials.[13] The included populations were well defined as women with an existing diagnosis of recurrent UTI who were more than 12 months from their last menstrual period. The two randomised controlled trials analysed contained only small patient numbers with differing results (relative risk 0.25, 95% confidence interval 0.13 to 0.50, and relative risk 0.64, 95% confidence interval 0.47 to 0.86), and therefore no robust recommendations can be made on the basis of such small scale trials. Adverse events for vaginal oestrogens were breast tenderness, vaginal bleeding or spotting, non-physiological discharge, vaginal irritation, burning, and itching. These side effects were reported in a minority of participants, but exact numbers were not described.[13]

An updated 2012 Cochrane review suggested that cranberry juice was less effective than previously indicated

Is ongoing research likely to provide relevant evidence?

More than 190 studies on recurrent UTI are listed on clinicaltrials.gov.[18] Emerging non-antibiotic prophylactic agents such as intravesical agents,[19] vaccines,[17] and D-mannose[20] show promise in reducing the risk of recurrent UTI, but have yet to be evaluated in robust randomised controlled trials. Further research is necessary to enable meaningful comparisons with prophylactic antibiotics.

A small meta-analysis of intravesical hyaluronic acid included four studies (two randomised, two non-randomised, 143 patients) looking at the use of this treatment in recurrent UTI, showing a statistically significant improvement in the rates of recurrent UTI (mean difference −3.4 episodes per patient year, 95% confidence interval −4.3 to −2.5).[19]

Vaginal vaccines (vaginal immunogens applied mucosally) have also been shown (three randomised controlled trials, 220 patients) to convey some benefit (relative risk 0.81, 95% confidence interval 0.68 to 0.96)[21] in reducing the risk of recurrent UTI, especially if the initial inoculation is followed up with booster doses. Smaller studies examining sublingual vaccines[20] and the use of D-mannose oral powder[14] have also shown promising results and have been compared directly with the current standard of prophylactic antibiotics.

RECOMMENDATIONS FOR FUTURE RESEARCH

Population: Female patients with recurrent UTI

Intervention: Prophylactic treatments to reduce/prevent infection

Comparison: Prophylactic antibiotics (current gold standard)

Outcome: Reduction in infection episodes, side effects of treatments, health economic analysis of cost effectiveness

Many of the studies in progress are small, and further research with larger numbers of participants is needed before any firm conclusions for prevention of recurrent UTI can be made. Specifically, new studies should be designed to examine patient reported outcomes and quality of life indices, as well as more conventional endpoints such as bacterial eradication. In addition, the use of current standard treatment of prophylactic antibiotics as a comparator should be encouraged, and studies should be designed to look at other endpoints such as antimicrobial resistance development as well as clinical benefit.

What should we do in the light of the uncertainty?

Based on the currently available evidence, prophylactic antibiotics remain the first line preventive treatment for uncomplicated recurrent UTI in women, and this is reflected in practice guidelines (Cochrane reviews, detailed in this article, have concluded that there is insufficient evidence to make a conclusive recommendation for many of the non-antibiotic treatments described).

Nonetheless, increased awareness of antimicrobial resistance has led patients and clinicians to seek alternatives. It has been noted that non-antibiotic prophylactic agents seem generally well tolerated, with few adverse events or side effects reported in the preliminary work described. Some of the non-antibiotic treatments—for example, vaginal oestrogens and probiotics, have been used extensively for other indications and therefore there are no concerns regarding their safety. As a result, there might be a case to support the use of non-antibiotic prophylactic agents, on an individual patient basis, for those who do not wish to take, or have an allergy or intolerance to, antibiotics.

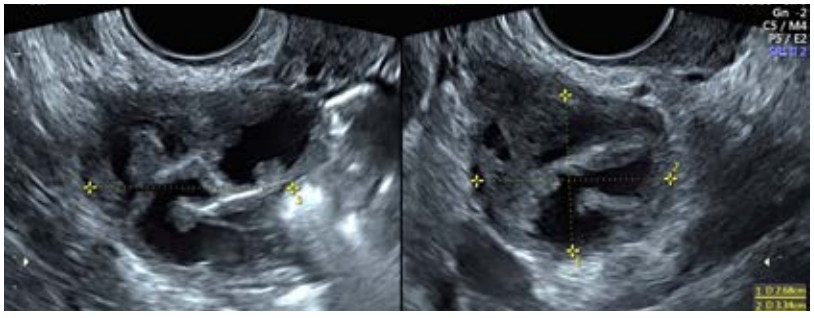
Competing interests: CH reports speaker fees from Astellas, Pfizer, Ferring, Allergan, Medtronic, and is a member of the advisory boards for American Medical Systems and Pierre Fabre Pharmaceuticals. JB and RV have no conflicts to report.

Cite this as: *BMJ* 2017;359:j5193

Find the full version with references at http://dx.doi.org/10.1136/bmj.j5193

CASE REVIEW

A teenage girl with lower abdominal pain



A 14 year old girl arrived with her mother at the emergency department complaining of a 6 day history of lower abdominal pain, associated with dysuria and mild fever. She reported no other symptoms. On examination, the girl was tender across the lower abdomen, particularly in the right lower quadrant, where mild guarding and rebound tenderness were present. She was given intravenous paracetamol.

During a brief private talk, she said she was sexually active with her boyfriend and was not using any form of contraception. Laboratory tests showed increased white blood count (13.6×10^9/L, neutrophils 8.7×10^9/L), C reactive protein of 5.4 mg/dL, and erythrocyte sedimentation rate of 47 mm/h. Beta-human chorionic gonadotropin levels were negative. Urine analysis showed mild leucocyturia.

An abdominal ultrasound showed normal appendix and ovaries, with a small amount of free pelvic fluid. Gynaecological physical examination showed cervical and uterine motion tenderness and vaginal discharge. A transvaginal ultrasound with colour Doppler analysis showed thickened, fluid filled fallopian tubes with hypervascularity (figure).

1 What is the most likely diagnosis?
2 How should this patient be managed?
3 What specific issues relate to managing this condition in adolescence?

Submitted by Chiara Zanchi, Cozzi Giorgio, Caterina Businelli, and Egidio Barbi

Parental consent obtained.

Cite this as: *BMJ* 2017;359:j5122

SPOT DIAGNOSIS

A man with paraesthesia, headache, and vertigo

A 35 year old man presented to hospital with three months' progressive paraesthesia of his right arm, leg, and torso. He also complained of intermittent headaches, particularly after coughing, and episodes of vertigo. Examination revealed hyperreflexia and numbness, with preserved joint position sense, in the right limbs. Magnetic resonance imaging was performed (fig 1). What is the diagnosis?

Submitted by Jacob O Day and Pragnesh Bhatt

Patient consent obtained.

Cite this as: *BMJ* 2017;359:j5165

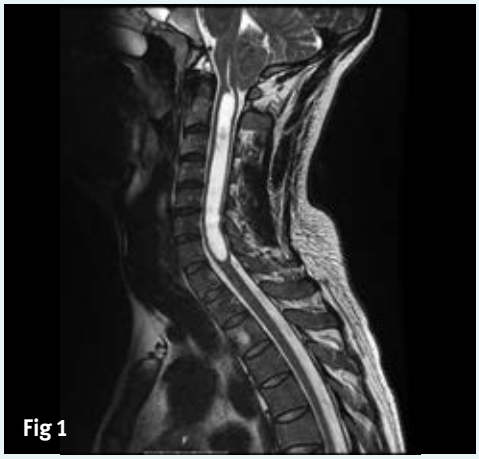


Fig 1

answers

CASE REVIEW

A teenage girl with lower abdominal pain

1 Pelvic inflammatory disease was diagnosed according to the diagnostic criteria stated by the 2015 Centers for Disease Control and Prevention guidelines for pelvic inflammatory disease.

2 The patient should receive antibiotic treatment consisting of a single dose of intramuscular ceftriaxone plus oral doxycycline 100 mg and metronidazole 500 mg every 12 hours for 14 days. She should be re-evaluated by a clinician within 72 hours to check her condition. Appropriate counselling about safe sexual behaviours is crucial, and tests should be performed for HIV and syphilis.

3 Adolescent girls with abdominal and genitourinary problems are most likely to visit a general practitioner or an emergency department; therefore physicians in these settings should consider pelvic inflammatory disease. Investigation should include an accurate history focusing on risk factors; this might require a private talk with the patient.

SPOT DIAGNOSIS

A man with paraesthesia, headache, and vertigo

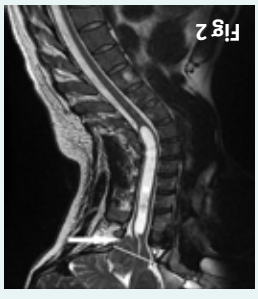


Fig 2

Chiari malformation type 1. The MRI scan shows tonsillar descent (arrow) characteristic of Chiari malformation type 1, and a resulting syringomyelia (fig 2).

CPD READING

0.5 HOURS

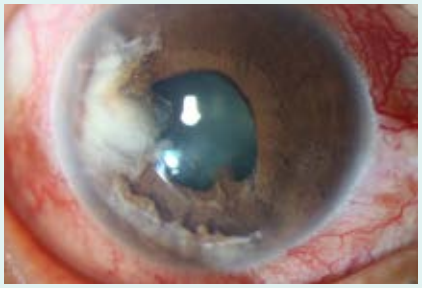
You can record CPD points for reading any article.
We suggest half an hour to read and reflect on each.

Metastatic adenocarcinoma masquerading as panuveitis

A 47 year old woman presented with redness, pain, blurred vision, and a fluffy mass in her right eye (figure). On examination, there was conjunctival congestion, keratic precipitates, retinal detachment, and ciliary body swelling, leading to a suspected diagnosis of panuveitis. On further questioning, she described a persistent cough and fatigue. Subsequent chest computed tomography and biopsy led to diagnosis of metastatic pulmonary adenocarcinoma masquerading as uveitis.

Masquerade syndromes are non-inflammatory disorders simulating uveitis. In one case series (n=828), they were diagnosed in 5% of patients with uveitis. In the same case series, 48% of masquerade syndromes were secondary to malignancy. This case highlights the importance of taking a complete history in patients with idiopathic uveitis.

Xiaohang Wu, Haotian Lin (gddlht@aliyun.com), Yizhi Liu, Zhongshan Ophthalmic Center, Sun Yat-sen University, China



Patient consent obtained.

Cite this as: *BMJ* 2017;359:j5071

Skin cancer among petroleum workers

High rates of skin cancer in petroleum workers can't be explained by occupational exposure to ultraviolet radiation while working offshore. Except for the face, the obligatory personal protective equipment covers all body parts. A study from Norway finds, however, that sunlight is still the major culprit— although the exposure probably occurs when workers are on leave (*Occup Med* doi:10.1093/occmed/kqx110). Long periods of being off duty and high incomes allow petroleum workers to enjoy outdoor activities and holidays in sunny destinations.

Z drugs and risk of falling

The National Institute for Health for Care Excellence reviewed the management of insomnia a few years ago. It reckoned that Z drugs (zaleplon, zolpidem, zopiclone, and eszopiclone) were no more effective than shorter acting benzodiazepines, and that there was no reason to believe their adverse effect profile was better. Even so, zopiclone has become the most frequently prescribed hypnotic in the UK. A systematic review in *Age and Ageing* finds that zopiclone and all Z drugs carry an increased risk of fractures and falls in elderly people (*Age Ageing* doi:10.1093/ageing/afx167).

Liver blood tests

Liver disease is becoming commoner and liver blood tests are ordered more often. The problem is that many patients with abnormal tests turn out not to have significant disease. On the other hand, because liver disease often develops without signs or symptoms, many people with late stage disease are still undiagnosed. The British Society of Gastroenterology has just issued guidance on which tests to ask for, when to ask for them, what constitutes an abnormality and, if they are found, what to do next (*Gut* doi:10.1136/gutjnl-2017-314924).

What difference will a minimum unit price for alcohol make?

As Scotland becomes the first country to set a minimum price for a unit of alcohol, Minerva was pleased to find some data on the issue. More than 600 patients who were either attending Scottish alcohol treatment services or in hospital with an alcohol related condition were asked about the sort of alcohol they bought and where they bought it. Their answers suggested that most alcohol was purchased at prices below the proposed minimum price of 50 pence per unit and that, if such a minimum price were imposed, many heavy drinkers would have to reduce their consumption (*Alcohol Alcoholism* doi:10.1093/alcalc/agx060).

Antioxidants and type 2 diabetes

Women whose diets included dark chocolate, tea, walnuts, prunes, and blueberries, which are all rich sources of antioxidant vitamins, were less likely to develop type 2 diabetes, according to a longitudinal study from France (*Diabetologia* doi:10.1007/s00125-017-4489-7). A protective effect from dietary antioxidants is not a new observation. Several epidemiological studies have linked them to reduced risk of cardiovascular disease and certain cancers. However, tested in randomised trials, vitamin supplements have failed to produce benefits. Indeed, there's some evidence that dietary supplements of β carotene and vitamins A and E might even increase mortality.

Intergenerational continuity of birth weight

It's well known that there's a modest correlation between the birth weights of mothers and their children. An analysis using the Aberdeen Maternity and Neonatal Databank adds another generation, finding that there is also a correlation between grandmothers' birth weights and the birth weights of their grandchildren (*Am J Epidemiol* doi:10.1093/aje/kwx340). The link is still present after taking account of socioeconomic and demographic factors. Many things run in families of course, so perhaps it's not surprising that fetal growth rate is among them.

Cite this as: *BMJ* 2017;359:j5336