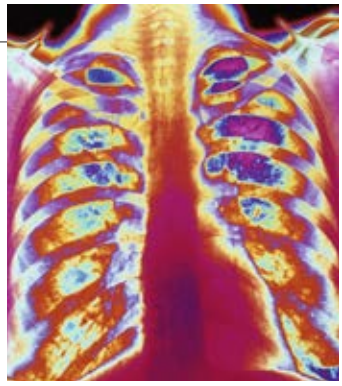
education

ART OF MEDICINE

Last orders, please



MEHAU KULYK/SPL

Semantics is the study of meaning. Words have denotations (literal meanings) and connotations (cultural or emotional associations). Words also have pragmatic or contextual meaning.

The denoted meaning of "order" is "an authoritative command or instruction." The connotation of the word is that the receiver is subordinate to the giver and that the action resulting from the order is not contingent on the receiver's agreement to undertake it.

"Order" therefore seems inappropriate for radiological requests, connoting that radiologists have no choice in whether procedures are carried out—undermining their role as consultants and gatekeepers. In 2007, the American College of Radiology's president said that allowing imaging studies to be treated as orders rather than consultation requests turns what radiologists do into a commodity.

Thoughts determine our words, but our words come to have lives of their own and influence our thoughts and behaviour.

Some will argue this is "just semantics." However, if we wish to emphasise our clinical consultant role in patient investigation and management and change the culture under which we practise, we should replace the word "order" with "request," "referral," or, better still, a request for consultation.

In our hospital, junior clinicians who utter the word "order" are sent away with fleas in their ears. They soon learn their error. Because these are the consultants of the future, we hope that the culture of "ordering" will be replaced by one of mutual respect and cooperation in the management of our patients.

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We welcome contributions to this column via our online editorial office: https://mc.manuscriptcentral.com/bmj.

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CLINICAL UPDATES

Lifelong annual HbA_{1c} tests for all women with gestational diabetes

All women who have had gestational diabetes should continue to be offered an annual HbA_{1c} blood test according to the latest Quality Standard from NICE. Regardless of postpartum and six week postnatal blood tests, these women remain at increased risk of developing type 2 diabetes. Earlier detection can slow disease progression and reduce future complication rates owing to earlier monitoring and treatment.

http://ow.ly/XFCp1

Green tea leaf extract used in treatment of genital warts

In November 2015 green tea leaf extract 10% ointment was licensed for use in the treatment of genital warts, a condition for which 130 000 people are treated in the UK each year. In a meta-analysis, it showed statistical significance in clearing warts within 16 weeks compared with placebo but has not yet been compared with existing topical treatments or ablative methods of wart removal.

http://bit.ly/1nCrH2m

Potential national screening programmes considered and rejected

The UK National Screening Committee reviewed the evidence but did not recommend screening for congenital adrenal hyperplasia in neonates, glaucoma, hearing loss in older people, mucopolysaccharidosis type 1, neuroblastoma in children, oral cancer, or prostate cancer. The committee already runs 11 population screening programmes and will regularly review new evidence.

http://bit.ly/1U03Ljf

FAST FACT—SELF HARM

Self harm remains a top five cause of admission to UK general medicine wards. It is the strongest predictor of future suicide, with a 30-fold increased risk in the four years after an episode compared with the general population. The risk of suicide is highest during the first week of inpatient admission and the first week of discharge. Risk must be explicitly considered on non-psychiatric wards with advice from the mental health team if concerns exist.

CPD/CME

You can gain CPD points from your reading by recording what you have read in your appraisal folder. You should try to link your reading back to a learning need and also consider how you plan to improve your practice as a result of your learning. http://learning.bmj.com

Are topical antibiotics an alternative to oral antibiotics for children with acute otitis media and ear discharge?

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Acute otitis media (AOM) is a common reason for childhood primary care visits and antibiotic prescription in the United Kingdom.[1 2] Many randomised controlled trials (RCTs) have shown that symptoms settle within a few days, irrespective of antibiotic use,[3] with one systematic review reporting that ear pain takes eight days to resolve fully in 90% of children.[4] However observational data and an individual patient data meta-analysis showed that, among children with AOM, those with ear discharge have a worse prognosis[5] and a more prolonged duration of ear pain or fever than those without ear discharge.[6] Current guidance from the UK National Institute for Health and Care Excellence recommends that general practitioners consider immediately prescribing oral antibiotics for children presenting with AOM and ear discharge.[7]

However, oral antibiotics commonly have side effects such as diarrhoea, vomiting, and rashes[3] and increase the risk of antimicrobial resistance.[8] For children with AOM and ear discharge, topical antibiotics are a possible alternative because they put less selective resistance pressure on bacteria and eardrum perforation allows direct entry of the antibiotic into the middle ear, without exposing children to systemic side effects.[9] However the risk of ototoxicity is debated.[10 11]

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Patient involvement was not sought for this article. However, we sought advice from a patient and public involvement group (including parents of children with ear infections) to formulate our research proposal. This group liked the idea of topical antibiotics as an alternative to oral treatment and thought that ear pain was the most important test of treatment effectiveness because of the distress it causes children and the disruption to family routines (sleep, work, and schooling).

What is the evidence of uncertainty?

To our knowledge, no RCTs or relevant systematic reviews of the effectiveness of topical antibiotics for children with AOM and ear discharge have been published.

Oral antibiotics

By contrast, individual patient data meta-analysis evidence shows that oral antibiotics are more effective than placebo or no treatment in reducing the duration of ear pain and fever in children with AOM and ear discharge; three children need to be treated with oral antibiotics to prevent one child experiencing ear pain or fever at 3-7 days.[6] However, these benefits should be weighed against the possible harms, including systemic side effects and increased risk of antimicrobial resistance.[3 8] For example, a systematic review reported that 27% of children taking oral antibiotics experienced vomiting, diarrhoea, or rash (283/1044), compared with 20% (208/1063) taking placebo.[3]

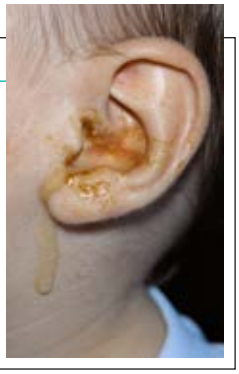
Topical antibiotics

A recent high quality RCT showed that antibiotic-glucocorticoid ear drops (not containing aminoglycosides) are clinically more effective and less costly than oral antibiotics in resolving ear discharge in children with grommets.[12 13] Because a grommet can be considered a surgically induced eardrum perforation, this indirectly suggests that topical antibiotics may be as effective as oral antibiotics for children with AOM presenting with ear discharge caused by spontaneous perforation of the eardrum.

Various topical antibiotic formulas are available in the UK, including those containing aminoglycosides, quinolones (such as ciprofloxacin with or without dexamethasone), and chloramphenicol. Of these,

WHAT YOU NEED TO KNOW

- Consider prescribing oral antibiotics immediately for children presenting with acute otitis media and ear discharge caused by spontaneous perforation of the eardrum
- Topical antibiotics are associated with fewer systemic side effects and a lower risk of antibiotic resistance than oral antibiotics, but there is no strong direct evidence to support their use in this condition



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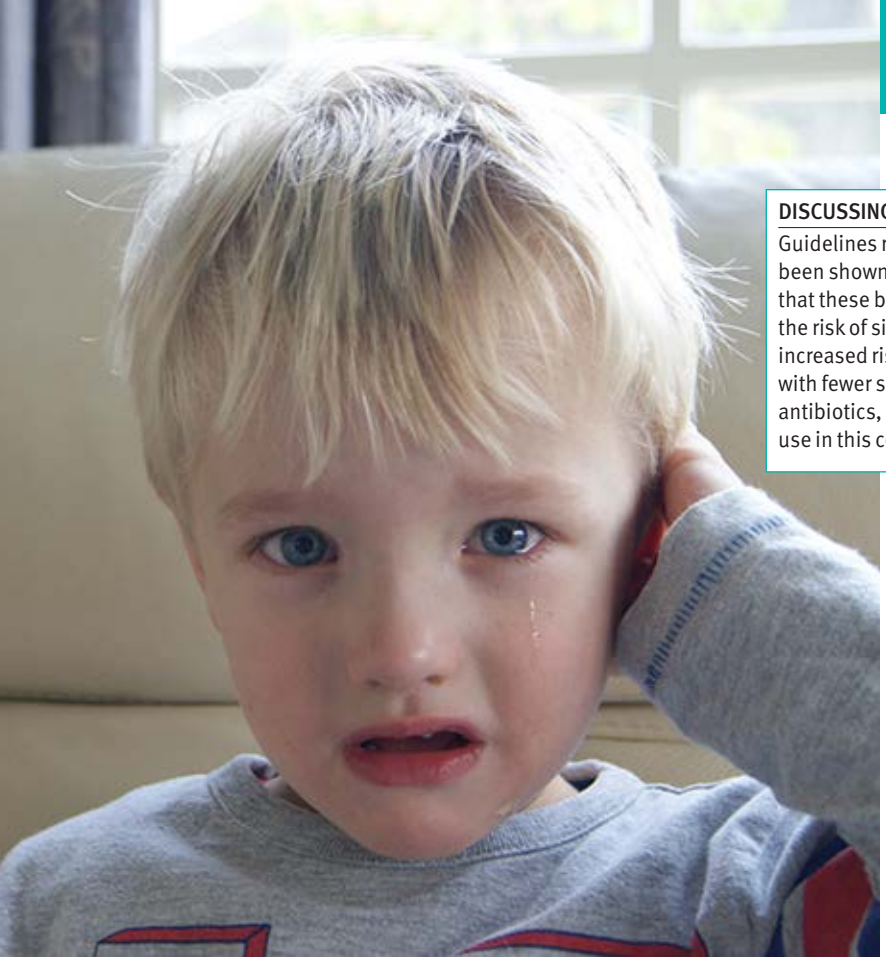

DISCUSSING THE UNCERTAINTY WITH PARENTS

Guidelines recommend immediately starting oral antibiotics as these have been shown to reduce the duration of ear pain and fever. However, explain that these benefits need to be balanced against possible harms including the risk of side effects, such as diarrhoea, vomiting, and rashes, and increased risk of antimicrobial resistance. Topical antibiotics are associated with fewer side effects and lower risk of antibiotic resistance than oral antibiotics, but there is currently no strong direct evidence to support their use in this condition.

quinolone containing drops are considered most appropriate because chloramphenicol has been known to cause sensitivity reactions in children and because of concerns about a link between aminoglycosides and ototoxicity. While animal studies have indicated that aminoglycoside antibiotics are potentially ototoxic when applied directly into the middle ear, the quality of the evidence in humans is debated. The risk of ototoxicity is generally thought to be low when topical antibiotics are used at the time of an active middle ear infection,[10] and there seems to be no such risk for quinolone containing drops.[9 10] The *British National Formulary* states that topical aminoglycosides or polymyxins are contraindicated in patients with perforated eardrums or patent ventilation tubes (grommets).[14] By contrast, a UK ear, nose, and throat consensus statement recommends: in "a patient with a discharging ear, in whom there is a perforation or patent grommet: if a topical aminoglycoside is used, this should only be in the presence of obvious infection…[and] for no longer than two weeks."[10]

Eardrum perforation allows direct entry of the antibiotic into the middle ear, without exposing children to systemic side effects

Is ongoing research likely to provide relevant evidence?

We searched the trial registries Netherlands Trial Register (NTR), ClinicalTrials.gov, ISRCTN Register, and metaRegister of Controlled Trials (mRCT) (on 1 June 2015) for completed or ongoing studies on this topic but found no relevant studies.

Our group has submitted grant proposals for two (UK and Netherlands) primary care based, pragmatic, open, two arm, individually randomised, non-inferiority controlled trials to compare the clinical and cost effectiveness of topical and oral antibiotics in children with AOM and ear discharge.

What should we do in the light of the uncertainty?

There is currently no strong direct evidence to support the use of topical antibiotics in children with AOM and ear discharge caused by spontaneous perforation of the eardrum. On the basis of current evidence, and in line with current guidance,[7] we recommend that doctors consider offering immediate oral antibiotics for these children. That said, doctors who are worried about the adverse effects of oral antibiotics could use the indirect evidence (from children with grommets) to justify the use of topical (non-aminoglycoside) antibiotics.[12 13] Although anecdotal, our experience suggests that for systemically well children with (otoscopic signs of) ear discharge but no ear pain, a delayed antibiotic strategy with advice about the natural course of the discharge (median duration four days)[15] may be appropriate.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: RPV has submitted a grant proposal on this topic to the Netherlands Organisation for Health Research and Development (ZonMw) and to the NIHR's HTA programme. ADH and VP submitted a grant proposal on this topic to the NIHR's HTA programme. ADH is a member of the NIHR HTA clinical evaluation and trials' board and chair of the National Institute for Health and Care Excellence antimicrobial stewardship guidelines development group.

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series advisers are Sera Tort, clinical editor, and David Tovey, editor in chief, the Cochrane Library. To suggest a topic for this series, please email us at uncertainties@bmj.com

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RECOMMENDATIONS FOR FURTHER RESEARCH

Population: children aged 6 months to 16 years with ear discharge caused by spontaneous perforation of the eardrum and ear pain as the presenting symptoms of acute otitis media (AOM)

Interventions and comparisons: topical antibiotics versus oral antibiotics

Primary outcome: ear pain

Secondary outcomes: duration and severity of systemic (fever, distress or crying, disturbed sleep, interference with normal activity, appetite) and ear (discharge, odour, hearing loss) symptoms; rescue analgesia; adverse events including serious AOM complications (such as mastoiditis, meningitis); recurrences of AOM; NHS resource use; disease specific quality of life using OMQ-14 (for younger children, this can be modified to ear problem related quality of life); antimicrobial resistance; parental satisfaction with treatment allocation and future desire to use ear drops

"No small talk please, my baby's just died"

A woman reflects on the ways healthcare professionals can help make miscarriage less devastating

ROSE LLOYD

CPD/CME
0.5 CREDITS

Thirteen years ago I was carrying a child that died at three months' gestation. I was 39 and I knew that a fair proportion of babies die early on in pregnancy. But there were things I wish the hospital staff had known, which might have helped them make this experience less devastating.

I had been on a walk along the Thames towpath when I registered a change in me. It was like a brief moment of awareness that a humming fridge has suddenly stopped and gone still. It was so fleeting that I immediately forgot about it.

A few days later I went to the local hospital's obstetric unit for my three month scan. A year earlier I'd nearly died during a ruptured ectopic pregnancy so I was pleased I'd made it this far. But the scan took longer than I imagined and I realised I was in trouble. Eventually a doctor came over to me and said he was sorry but they had been unable to find a heartbeat. He said some other things that I couldn't take in.

It matters where you wait

I was ushered back into the waiting room area and told to wait until someone could see me to talk through what to do next. The waiting room was teeming with expectant mothers who were feeding babies and entertaining bored toddlers. It is difficult to describe exactly how bad I felt sitting among all this lively commotion. Here were dozens of heavily pregnant mothers literally bursting with life and my belly had just become a giant watery tomb.

Every hour I waited, the urge to get up and run grew stronger. I kept repeating "I'd like to go home now please" but the nurse insisted I needed to wait and that a doctor would come to see me soon. I felt so upset that it didn't even occur to me to ask whether I could sit somewhere else.

> It was like a brief moment of awareness that a humming fridge has suddenly stopped

Small talk

Finally, after about four hours (it was a busy day) a young doctor led me into her office to talk through my options for how to end the pregnancy. I was trying to remain calm and not show how dreadful I was feeling so I smiled at her. She asked me what I did for a living. I was a radio producer, I told her. "Oh, that's interesting", she said, "is it hard to get your ideas made into programmes?" I tried to answer, but my mouth was dry and I was on the brink of tears. What I really wanted at that moment was someone who would reassure me, perhaps ask me if I wanted a hug. Someone who would explain in simple terms that I could either have the fetus removed surgically or take some pills that would expel it in a few days. I was not able to follow the medical jargon the keen young doctor used to discuss my options. I just wanted to go home and cry.

For series information contact Rosamund Snow, patient editor, rsnow@bmj.com

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WHAT YOU NEED TO KNOW

- It would have made an enormous difference to me to be able to wait in a different environment, especially as the wait was so long. Even just waiting in a corridor around the corner from all the pregnant women would have been a whole lot more bearable
- Not all patients like to talk about their jobs when they've just been given the bad news that their baby has died. A word of sympathy, or even silence, would have been more welcome. Anything, just not having to make small talk
- Too much information, especially if the patient has just had some shocking news, can be counterproductive. If patients are on their own, give them the option of talking through the details on the phone later when they have had some time to assimilate what's happened

SUPPORT GROUPS THAT CAN HELP YOUR PATIENT

Miscarriage Association (www.miscarriageassociation.org.uk)
Mumsnet (www.mumsnet.com/info/search?query=miscarriage)
NCT (www.nct.org.uk/pregnancy/miscarriage)

Management of psychotropic drugs during pregnancy

CPD/CME
1 CREDIT

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SUMMARY

Psychiatric conditions (including substance misuse disorders) are serious, potentially life threatening illnesses that can be successfully treated by psychotropic drugs, even during pregnancy. Because few rigorously designed prospective studies have examined the safety of these drugs during pregnancy, the default clinical recommendation has been to discontinue them, especially during the first trimester. However, in the past decade, as more evidence has accumulated, it seems that most psychotropic drugs are relatively safe to use in pregnancy and that not using them when indicated for serious psychiatric illness poses a greater risk to both mother and child, including tragic outcomes like suicide and infanticide.

Incidence and prevalence

At one time pregnancy was thought to protect against psychiatric illness, particularly depression.[1 2] However, for women with pre-existing psychiatric conditions (including substance misuse disorders), pregnancy and the postpartum are vulnerable periods when psychiatric illness may worsen or relapse. About 15% of pregnant women have a psychiatric illness and 10-13% of fetuses are exposed to a psychotropic drug.[3 4] Women with psychiatric disorders can experience relapse during pregnancy, even when they are taking the appropriate drugs.

Controversies and limitations of the literature

Few studies have been conducted to determine which drugs for treating psychiatric disorders are efficacious during pregnancy, how changes in body weight and metabolism may affect dosing, and what long term effects these drug have on the developing fetus.

Abrupt discontinuation of psychotropic drugs can result in withdrawal symptoms and relapse of psychiatric illness, and several studies have shown that exposure to psychiatric illness in utero results in poorer outcomes for mother and child.

Diabetes, obesity, smoking, and substance misuse are more common in people with psychiatric illness than in the general population. Studies that have not controlled for the underlying psychiatric illness and its risks may find associations between psychotropic drugs and outcomes that are not caused by exposure to the drug itself, but by the presence of other risk factors.

Changes in metabolism and drug clearance during pregnancy

Physiologic changes occur in a woman's gastrointestinal system, cardiovascular system, renal system, and other systems during pregnancy. Changes affect the pharmacokinetic processes of drug absorption, distribution, metabolism, and excretion. Renal blood flow, glomerular filtration rate, and elimination of drugs also increase,[27] and changes in liver enzyme activation occur (for example, CYP1A2 activity decreases; CYP2D6 activity and CYP3A activity increase). These liver enzyme changes, which are mostly hormone dependent, can either increase or decrease the clearance of drugs.

All psychotropic drugs can move from the maternal to the placental system. The use of multiple drugs carries additional risks (for example, drug-drug interactions, induction or inhibition of metabolic pathways, adverse effects in pregnancy of concomitantly used licit or illicit drugs).

Serotonin reuptake inhibitors

Teratogenesis

A small increase in the absolute risk of rare defects with exposure to SSRIs has been reported,[34] but four meta-analyses examining the risk of major malformations with exposure to SSRIs in the first trimester found no significantly increased risk.[35-38] Data on other types of antidepressant are limited. Most studies examining the risks of tricyclic antidepressants have found no increased risk of malformations,[39-43] although one large epidemiological study found a significant increase in severe malformations (odds ratio 1.36, 95% confidence interval 1.07 to 1.72).[44] With the possible exception of heart defects (see below), several studies of bupropion have found no association with major malformations.[45-47] The data available for other types of antidepressants are small but reassuring.[48 49]

WHAT YOU NEED TO KNOW

- For women with pre-existing psychiatric conditions, pregnancy and the postpartum are vulnerable periods when psychiatric illness may worsen or relapse.
- Abrupt discontinuation of psychotropic drugs can result in withdrawal symptoms and relapse of psychiatric illness, and several studies have shown that exposure to psychiatric illness in utero results in poorer outcomes for mother and child.
- Given the data indicating that psychiatric illness poses risks for both the mother and child, the treatment priority should be to keep the mother psychiatrically well during pregnancy.
- Large, well designed and controlled studies have shown that most classes of psychotropic drugs seem to be relatively safe during pregnancy.
- Untreated psychiatric disorders during pregnancy have associated risks for both mother and child and these risks need to be considered in the risk-benefit analysis of psychotropic drug use during pregnancy.

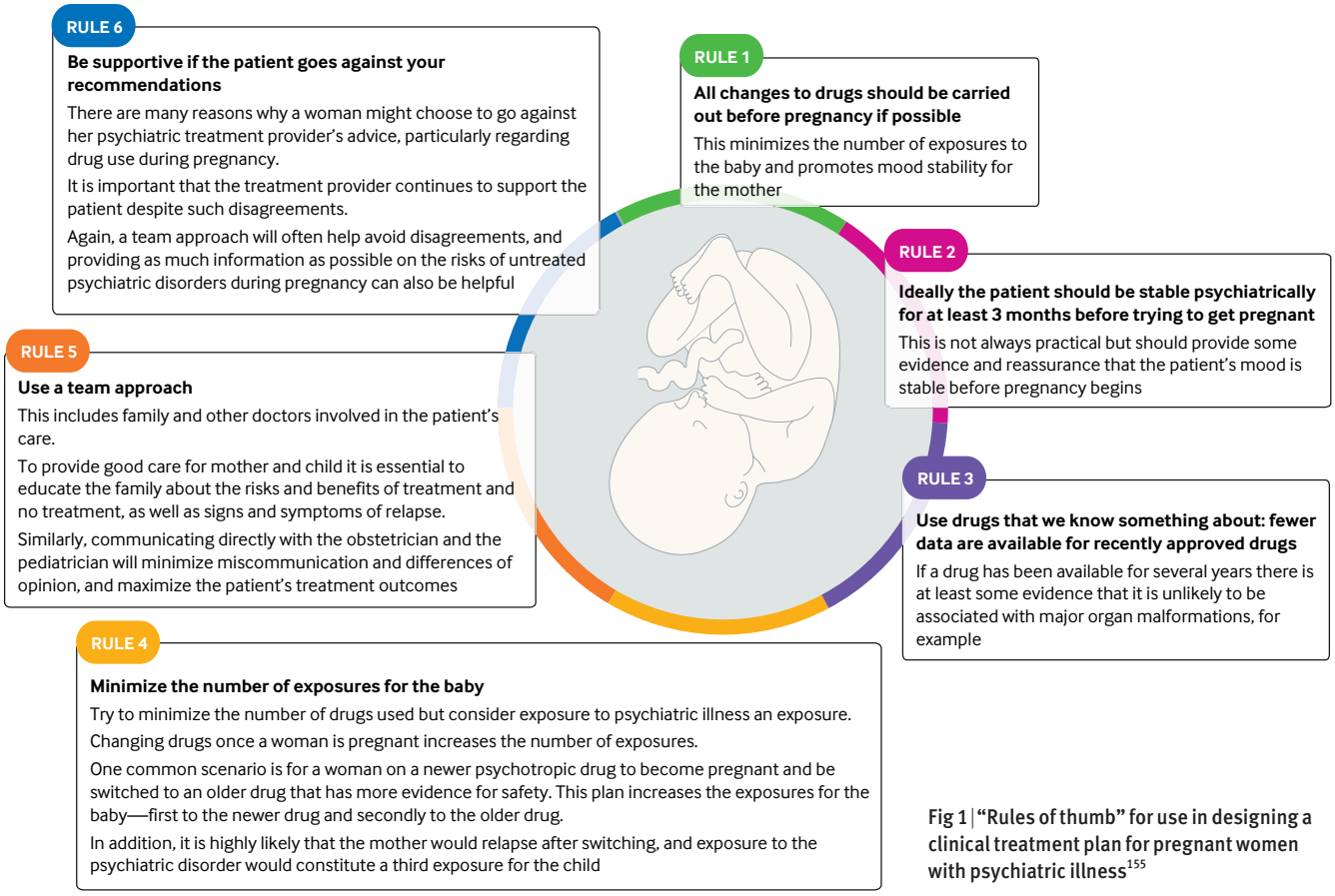


Fig 1 | "Rules of thumb" for use in designing a clinical treatment plan for pregnant women with psychiatric illness[155]

Cardiovascular malformations

Studies have reported no consistent association between the use of antidepressants during pregnancy and cardiovascular malformations. Use of paroxetine during the first trimester has been associated with a higher risk of cardiac malformations in some studies,[46 50 51] but not in others.[34 52] Studies of bupropion have also yielded conflicting results.

The overall consensus is that the risk of major organ malformations, if it exists, is small in the setting of antidepressant monotherapy.[55]

Several studies have shown that the association between antidepressants and cardiac defects is probably secondary to underlying risk factors in people with depression. The largest study to date (>900 000 women)[57] found no association between first trimester antidepressant exposure and cardiac malformations when the analyses controlled for the underlying illness, depression. Finally, a meta-analysis of prospective cohort studies found no association between SSRI use in the first trimester and heart defects.[58]

Spontaneous abortion

Overall results suggest that the use of antidepressants in early pregnancy is associated with a modestly raised risk of spontaneous abortion.[49 59-61]

Preterm birth and birth weight

Overall, the literature suggests that the rate of preterm birth is higher among mothers who take antidepressants. However, most studies did not control for the severity of psychiatric illness and other confounding variables found more commonly in those with psychiatric disorders.[48 49]

Poor neonatal adaptation syndrome (PNAS)

The FDA instituted a class labeling change in 2004 for SSRI and SNRI (serotonin-norepinephrine (noradrenaline) reuptake inhibitor) antidepressants warning that third trimester exposure may be associated with PNAS. According to the label change, "reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyper-reflexia, tremor, jitteriness, irritability, and constant crying."

Larger, more rigorous studies of the syndrome and strategies to reduce the occurrence of the syndrome are needed. There is currently insufficient evidence from a safety perspective to recommend tapering antidepressants in the third trimester, particularly in cases of moderate to severe maternal mental illness.

Autism

Several studies have looked at the association between SSRI use during pregnancy and autism spectrum disorders (ASDs). In a case control study[78], antidepressant use in the year before delivery was associated with double the risk of ASD in the offspring (odds ratio 2.0, 1.2 to 3.6), with the strongest effect found with first trimester exposure (3.5, 1.5 to 7.9). Risk was not increased in children of mothers with a history of mental health treatment who did not use antidepressants during pregnancy.

A nested case-control study examined maternal and paternal depression and antidepressant use during early pregnancy and the risk of ASD in a Swedish cohort of more than 500 000 children.[79] Maternal depression was associated with an increased risk of ASD (1.49, 1.08 to 2.08), whereas paternal depression was not (1.21, 0.75 to 1.96). Maternal depression and antidepressant use did not increase the risk of ASD with intellectual disability but did increase the risk of ASD without intellectual

LEVEL A

Based on good and consistent scientific evidence

- Lithium exposure in pregnancy may be associated with a small increase in congenital cardiac malformations, with a risk ratio of 1.2 to 7.7
- Valproate exposure in pregnancy is associated with an increased risk of fetal anomalies, including neural tube defects, fetal valproate syndrome, and long term adverse neurocognitive effects. It should be avoided in pregnancy, if possible, especially during the first trimester
- Carbamazepine exposure in pregnancy is associated with fetal carbamazepine syndrome. It should be avoided in pregnancy, if possible, especially during the first trimester
- Maternal benzodiazepine use shortly before delivery is associated with floppy infant syndrome

LEVEL B

Based on limited or inconsistent scientific evidence

- Avoid using paroxetine, if possible, in pregnant women and women planning pregnancy. Consider fetal echocardiography for women who are exposed to paroxetine in early pregnancy
- Prenatal benzodiazepine exposure increased the risk of oral cleft, although the absolute risk increased by only 0.01%
- Lamotrigine is a potential option for maintenance therapy in pregnant women with bipolar disorder because of its protective effects against bipolar depression, general tolerability, and a growing reproductive safety profile relative to alternative mood stabilizers
- If inadequately treated or left untreated, maternal psychiatric illness may result in poor compliance with prenatal care, inadequate nutrition, exposure to additional drugs or herbal remedies, increased use of alcohol and tobacco, deficits in mother-infant bonding, and disruptions within the family environment

LEVEL C

Based primarily on consensus and expert opinion

- Whenever possible, multidisciplinary management involving the patient's obstetrician, mental health clinician, primary healthcare provider, and pediatrician is recommended to facilitate care
- Use of a single drug at a higher dose is favored over the use of multiple drugs for the treatment of psychiatric illness during pregnancy
- The physiologic changes of pregnancy may affect the absorption, distribution, metabolism, and elimination of lithium, so close monitoring of lithium levels is recommended during pregnancy and in the postpartum period
- Individualize treatment with all selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors, or both, during pregnancy
- Consider fetal assessment with fetal echocardiography in pregnant women exposed to lithium in the 1st trimester

LEVELS OF RECOMMENDATIONS

LEVEL A	LEVEL B	LEVEL C
Recommendations are based on good and consistent scientific evidence	Recommendations are based on limited or inconsistent scientific evidence	Recommendations ar based primarily on consensus and expert opinione

Fig 2 | Major recommendations from the American College of Obstetricians and Gynecologists (ACOG),[155] according to the level of evidence

disability (4.95, 1.85 to 13.23), although not in the absence of maternal depression (2.1, 0.97 to 4.57). This study did not control for the underlying psychiatric illness.

In a Danish cohort study,[80] compared with women who had never used SSRIs, use of SSRIs during pregnancy was not associated with an increased risk of ASD (1.20, 0.90 to 1.61). By contrast, the odds ratio for women who received SSRIs before but not during pregnancy was 1.46 (1.17 to 1.81), indicating that the risk is probably due to the underlying illness (depression) and not the use of antidepressants.

Mood stabilizers

Lamotrigine

The North American antiepileptic drug pregnancy registry found that infants who are exposed to lamotrigine monotherapy during pregnancy have a much higher risk of oral cleft defects with a 10.4 fold increase (4.3 to 24.9).[82] However, a large study published in 2008 found no association.[83] Lamotrigine levels may decrease over the course of pregnancy and thus should be monitored and adjusted if needed.[84]

Valproic acid

First trimester exposure to valproic acid is associated with a high rate of malformations (≤10%) including neural tube defects, effects on cognition and brain volume, craniofacial anomalies, cardiac defects, cleft palate, and hypospadias.[62] Exposure to valproic acid has also been recently linked with autism in two studies.[85 86] Providers should encourage pregnant women who want to continue taking an anticonvulsant to take high dose folate (4 mg/day), and to undergo a second trimester ultrasound to screen for major congenital anomalies. Blood levels of valproic acid should also be monitored.

Carbamazepine

Carbamazepine also carries an increased risk of malformations, primarily of spina bifida and other neural tube defects, as well as facial abnormalities, skeletal abnormalities, hypospadias, and diaphragmatic hernia.[62] Because carbamazepine is a competitive inhibitor of prothrombin precursors, it may also increase the risk of neonatal hemorrhage. High dose folate should be taken and screening for malformations and therapeutic blood monitoring should be carried out.

Lithium

Lithium use during the first trimester has been associated with an increased risk of a serious congenital heart defect known as Ebstein's anomaly, which occurs in about 1/1000 live births. The risk of Ebstein's anomaly with first trimester exposure was originally thought to be much higher (400 times higher) than baseline, but a pooled analysis of lithium exposed pregnancies found that this defect occurred in only 1/1000-1/2000 exposed children.[87] This translates to greater than 99% of exposed children not developing this anomaly.

Lithium has also been associated with perinatal toxicity, including case reports of hypotonia, cyanosis, neonatal goiter, and diabetes insipidus. For women with severe bipolar disorder, the risk of recurrence during

pregnancy may overshadow the relatively small risk of Ebstein's anomaly. For such women, maintenance lithium therapy during pregnancy may be the most appropriate course. By contrast, for women with periods of euthymia and few past mood episodes, slow tapering of lithium and reintroduction after the first trimester may help reduce the risk of relapse during the postpartum period.

Lithium levels should be followed closely during pregnancy and the dose should be held or reduced with the initiation of labor. Hydration during delivery should be adequate and the dosage reduced to pre-pregnancy levels (if it was increased during pregnancy), with close monitoring of serum levels.[62]

Antipsychotics

A systematic review published in 2004 on the use of antipsychotics for primary (non-affective) psychosis in pregnancy concluded that "continued use of antipsychotic drugs in these women in pregnancy and lactation without sound evidence raises serious clinical and ethical concerns."[89] However, as more evidence has accumulated, it seems that antipsychotics are relatively safe in pregnancy and that not using them when indicated for serious mental illness poses a much greater risk, including the grave risks of suicide and infanticide.[90]

With advancing pregnancy, CYP1A2 enzymes are downregulated, doses of olanzapine and clozapine may need to be decreased, while doses of drugs that are metabolized by upregulated enzymes may need to be increased.[93] Placental transfer from mother to fetus is lowest for quetiapine, risperidone, haloperidol, and olanzapine.[94]

Many antipsychotics, particularly second generation antipsychotics (SGAs), are associated with excessive maternal weight gain, increased infant birth weight, and increased risk of gestational diabetes.[93 95] Routine ultrasound monitoring of fetal size in late pregnancy may be beneficial in women who are taking these drugs.[95 98]

Motor restlessness, dystonia, hypertonia, and tremor have been noted in infants exposed to antipsychotics in utero.[96 99] The few studies examining the association between in utero exposure to first generation antipsychotics (FGAs) and neurodevelopment have shown no difference in IQ or behavioral functioning at 5 years.[9 100 101] Studies of SGAs have shown associated neurodevelopmental delays at 6 months of age.[102 103] However, a case-control prospective study found that these delays were no longer evident at 12 months.[62 102]

Antianxiety agents

Benzodiazepines

Benzodiazepine use during pregnancy has been associated with case reports of perinatal toxicity, including temperature dysregulation, apnea, reduced Apgar scores, hypotonia, and poor feeding. In addition, early studies identified an increased risk of oral cleft palate defects. However, more recent prospective and retrospective studies have shown no increased risk of cleft lip or palate with benzodiazepine use in pregnancy.[110 111] On the basis of population based health data, infants exposed to an SSRI in combination with a benzodiazepine may have a higher incidence of congenital heart defects even when controlling for maternal illness characteristics (adjusted odds ratio 1.18, 0.18 to 2.18).[112]

Gabapentin

Several studies have indicated that there is no increased risk of major congenital malformations with gabapentin.[113 114] A more recent study published in 2013 also found no increased risk of malformations but found higher rates of preterm birth, low birth weight, and admission to neonatal intensive care.[115]

Pregabalin

This is less well studied than gabapentin but there is currently no known association with an increased risk of malformations.

Medication assisted treatment for substance dependence

Methadone

Methadone exposure puts neonates at risk of neonatal abstinence syndrome (NAS). Most neonates with NAS require inpatient detoxification, often in an intensive care unit. Little is known about long term neurodevelopmental outcomes in these neonates, although several longitudinal studies have shown no differences in cognitive performance in adult children of opioid dependent mothers receiving methadone compared with children of matched maternal controls.[128]

Buprenorphine

Studies suggest that methadone may be superior for maternal treatment retention but that NAS may be shorter in infants whose mothers use buprenorphine.[132] Although studies suggest that both methadone and buprenorphine are safe for use in pregnant women,[133-135] they do not support a shift from methadone to buprenorphine for methadone treated patients who become pregnant.[130 136-138]

Antihistamines

A systematic review published in 2014 of antihistamines and birth defects identified two cohort (n=31) and eight case-control (n=23) studies that found an association between prenatal antihistamine exposure and congenital malformations.[142]

Although more than 90% of pregnant women report using over the counter antihistamines to treat insomnia,[144] a recent systematic review of the use of sleep promoting drugs during pregnancy identified only two studies on prenatal antihistamine exposure.[145] One found no association between exposure and congenital malformations,[54] and the other examined sleep and mood outcomes.[146] Sleep agents including eszopiclone, ramelteon, and zolpidem have not been associated with major organ malformations,[145] but zolpidem use for longer than 90 days has been associated with an increased risk of low birth weight (odds ratio 1.39, 1.17 to 1.64), preterm birth (1.49, 1.28 to 1.74), and cesarean delivery (1.74, 1.59 to 1.90).[147]

General approach to the management of psychotropic drugs during pregnancy

Ideally, plans for the treatment of a patient's psychiatric disorder during pregnancy should be in place before the woman becomes pregnant. However, as many as 50% of pregnancies are unplanned in the US,[154] so practitioners often need to make treatment decisions for patients who are already pregnant. The treatment priority should be to keep the mother psychiatrically well during pregnancy. Every case should be considered individually. The patient's psychiatric history, severity of symptoms, response to drugs, and wishes regarding drug use during pregnancy all play an important role in designing a course of clinical care during pregnancy. Figure 1 shows the "rules of thumb" for designing a clinical treatment plan for pregnant women with psychiatric illness.

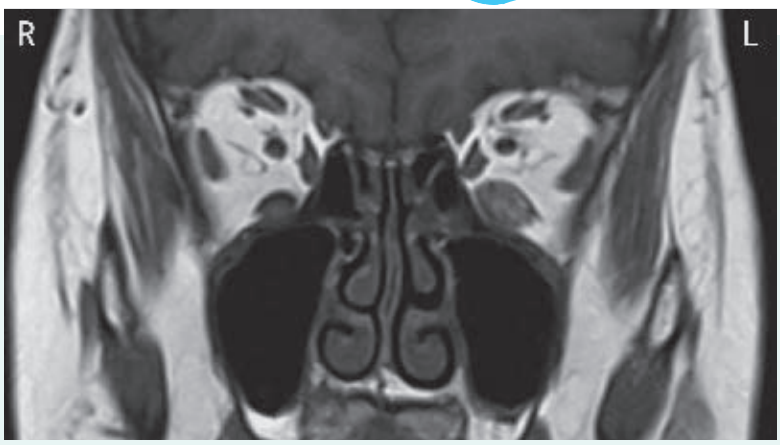
Guidelines

ACOG issued "Guidelines on the use of psychotropic medications during pregnancy and lactation" in 2008 and reaffirmed them in 2012.[156] Figure 2 lists the main recommendations. In 2014, the National Institute for Health and Care Excellence also issued guidelines on the clinical management of antenatal and postnatal mental health.[157]

SPOT DIAGNOSIS

A case of double vision

A 55 year old woman who had recently been treated for thyrotoxicosis presented with double vision. She had left sided hypotropia and slight exophthalmos in an otherwise normal ophthalmological and neurological examination. What abnormality is seen in this coronal T1 weighted orbital magnetic resonance image?



Submitted by James Lowe and David C Howlett
Patient consent obtained.
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Find this at: http://dx.doi.org/10.1136/bmj.h6706

CASE REVIEW

Management of ankle injuries

A 26 year old woman presented to the emergency department after injuring her left ankle. While walking on an uneven pavement in the rain she lost her footing and described a sudden "buckling" of her ankle (plantar flexion and inversion injury). She could not bear weight so an ambulance was called.

She was previously fit and well and was on no regular drugs. Six months earlier she had twisted the same ankle while playing hockey. Radiographs taken at the emergency department had been normal, and she was discharged with crutches and a compression bandage. She returned to work after two weeks but had not returned to sport because she did not trust her ankle.

Clinical examination identified tenderness, swelling, and ecchymosis over the anterior talofibular and calcaneofibular ligaments, with some bony tenderness on the posterior edge of the lateral malleolus. She had no medial tenderness. Ankle ligament stress testing was not performed owing to pain.

1 What is the most likely diagnosis?
2 What are the other possible diagnoses after this mechanism of injury?
3 What relevant history and examination are needed?
4 How should she be investigated?
5 How should she be managed?
6 What features warrant specialist referral in patients with ankle sprain presenting to general practice?
7 How should she be followed up?

Submitted by Matthew Welck, Michael Rafferty, Stephanie Eltz, Shafic Said Al-Nammari, and Kelechi Chika Eseonu
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answers

SPOT DIAGNOSIS
A case of double vision

Isolated enlargement of the left inferior rectus muscle secondary to thyroid eye disease.

CASE REVIEW
Management of ankle injuries

1 Lateral ankle ligamentous injury.
2 Ankle fracture, anterior calcaneal tuberosity fracture, fifth metatarsal fracture, syndesmosis injury, ankle osteochondral injury, and peroneal tendon injury.
3 History must include details of the injury, current symptoms, and previous injuries. Examination comprises "look, feel, move, special tests." The anterior drawer and talar tilt tests assess the lateral ligamentous complex.
4 Because she was unable to bear weight and had bony tenderness at the posterior edge of the lateral malleolus, radiography of the ankle is warranted.
5 She may need a boot or brace, cryotherapy, elevation, and analgesia initially. Encourage weight bearing and start range of motion exercises when pain allows, progressing to concentric and eccentric strengthening, proprioceptive training, and sport rehabilitation.
6 Concerns about fracture, osteochondral injury, neurovascular compromise, tendon rupture or subluxation, or syndesmosis injury in acute presentations. Persistent instability, recurrent instability, and persistent pain after completion of rehabilitation.
7 Evaluation at two weeks and then three months.

We welcome contributions that would help doctors with postgraduate examinations. We also welcome submissions relevant to primary care.
See thebmj.com/endgames

Dystrophic nails

A 98 year old female nursing home resident was referred with suspected onychomycosis (fungal nail infection). Nine residents and staff had been treated for recurrent scabies. This patient had received topical permethrin on three occasions. She had massive subungual hyperkeratosis and widespread scaly skin. Scabies mites were seen on dermoscopy. A diagnosis of Norwegian scabies was made and she was treated with two doses of oral ivermectin (200 µg/kg) seven days apart, plus topical permethrin. At three months her skin was clear and nail architecture was returning to normal. Unlike typical infestations, Norwegian scabies is highly infectious and topical treatment alone is often insufficient; if left untreated it can lead to widespread outbreaks.

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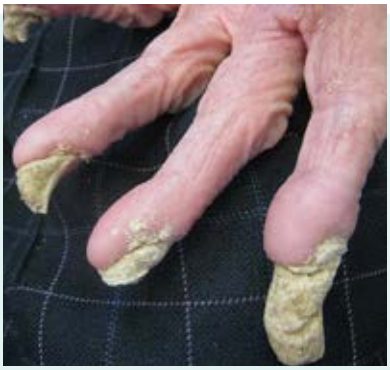


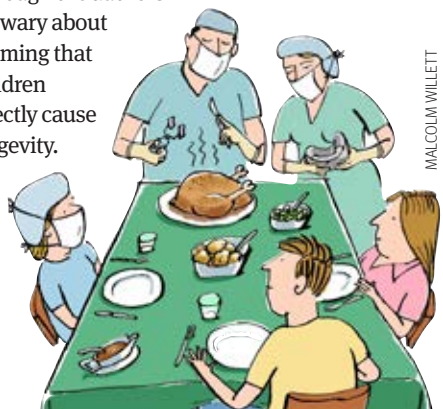
Great news on births

Rates of stillbirths and neonatal deaths dropped across the whole of Europe between 2004 and 2010, according to data from the Euro-Peristat project (*J Epidemiol Community Health* doi:10.1136/jech-2015-207013). This applied equally to countries with high or low rates, meaning that everyone is doing something better. The challenge is to share lessons and embed them in practice.

Rates of stillbirths and neonatal deaths dropped across the whole of Europe between 2004 and 2010

Location, vocation, procreation

A study of 3068 obituaries from *The BMJ* between 2003 and 2012 compares age at death with medical specialty, region (deanery), marriage status, and number of children (*Occup Med (Lond)* doi:10.1093/occmed/kqv207). Doctors who went into public health, obstetrics and gynaecology, and laboratory medicine all tended to live longer. So did doctors with children, although the authors are wary about claiming that children directly cause longevity.



MALCOLM WILLETT

Another inverse care law

A survey of nearly 30 000 Danish citizens shows that, compared with others, people with long term conditions report more difficulties in understanding health information and engaging with healthcare providers (*BMJ Open* doi:10.1136/bmjopen-2015-009627). It's another inverse care law—the greater the disease burden, the more obstacles there are to coping with it.

Failure: the price of MI success

Myocardial infarction (MI) is becoming less common, but the risk of heart failure in MI survivors is probably staying constant. Data from the whole population of Norway (CVDNOR; *J Am Heart Assoc* doi:10.1161/JAHA.115.002667) show that deaths from post-MI heart failure increase with age, and that the risk over subsequent years is also much higher in those over 75.

Sharing last ditch cancer options

Decisions about second or third line chemotherapy for cancer are about trade-offs between longer survival and quality of remaining life. Eliciting patient preferences and sharing information would seem to be vital in this situation, but an interview study of 28 Dutch patients with cancer shows how infrequently this happens (*Health Expectations* doi:10.1111/hex.12434).

Right bandwidth for knee pain?

A wearable pulsed electromagnetic fields device has been tested against a sham device in 60 Italian patients with pain caused by knee osteoarthritis (*Rheumatology* doi:10.1093/rheumatology/kev426). The non-ionising radiofrequency energy seemed to help, although further trials will be needed before this treatment can be broadcast more widely.

OSCEs: just acting?

The practice of using actors to simulate patients and assess communication skills in the objective structured clinical examination (OSCE) is subjected to sociolinguistic analysis in a new study (*BMC Med Educ* doi:10.1186/s12909-016-0535-2). Students can "feel crass" in these artificial encounters, which probably are not an ideal way to judge real life communication, although the authors deny any wish to "bury OSCEs" completely.

Why don't you just SPLEEN-OFF

SPLEEN-OFF is not an expression Minerva has heard before, in anger or otherwise. It is the name of a group studying overwhelming infections in people who have undergone splenectomy (*Clin Infect Dis* doi:10.1093/cid/civ1195). *Streptococcus pneumoniae* remains the leading pathogen, causing 42% of cases reaching intensive care units in Germany. Fewer than half these patients had received pneumococcal vaccination.

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