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Twelve covid-19 autopsies
Venous thromboembolism has been recognised as a major part of covid-19 pathology. Wichmann and colleagues’ cohort study of the first 12 consecutive covid-19 positive patients who died in Hamburg, Germany, confirms this. Full autopsies were conducted, including postmortem computed tomography. The cause of death in four cases was massive pulmonary embolism with deep venous thromboses in the lower limbs. A further three cases had deep vein thromboses that had not been suspected before death. Eleven cases had pre-existing heart disease.

This points towards an important role for coagulopathy in this condition and gives some credence to a strategy of anticoagulation. As for the lungs, the histopathology showed diffuse alveolar damage which is consistent with difficulties ventilating.

Dude, where’s my immunity passport?
Actually, I don’t really want the UK to adopt this approach. It’s discriminatory. Why should only immune people get to travel/work/go about their business? It even penalises those who have been adhering to strict social distancing.

Hall and colleagues point out many of the issues in their letter. For example, they explain that understanding of immunity from the virus is “fairly rudimentary.” That’s an understatement. Not knowing the duration or level of immunity that comes with a positive IgG result is fairly disastrous for an immunity “passport” system. The authors also discuss the challenge of providing access to reliable tests on which to base such a system.

In summary, while some parts of the world may end up using such a system to varying extents, particularly for healthcare workers, it doesn’t seem to have legs. If I had to speak in favour of this system, I would say that, at least it could mean less restriction than full lockdown.

Meeting in the muddle
Hung and colleagues randomised 127 patients with mild to moderate covid-19 in Hong Kong in an open-label trial. Both groups received lopinavir and ritonavir. One group also got interferon beta-1b and ribavirin. The aim was to reduce the time to a negative SARS-CoV-2 PCR result on a nasopharyngeal swab. There was convincing and statistically significant evidence that the treatment group had a shorter time to a negative swab (a median of seven days versus 12 days). It’s a bit weird that both groups got some background antivirals that aren’t backed up with randomised evidence. Perhaps this was a pragmatic decision because clinicians are susceptible to the “something is better than nothing” fallacy and therefore would not be happy to randomise people to a control group that gets no treatment.

We humans can be so illogical sometimes. We fear that depriving patients of a treatment that might help is worse than not giving that treatment even if the treatment has no evidence base and could in fact do harm. And this fear overrides our desire for the rigour of randomised trials.

Nevertheless, this study was randomised and therefore has some value in supporting the use of triple antiviral therapy and interferon over lopinavir and ritonavir alone. This may be challenging to translate into practice because lopinavir-ritonavir isn’t necessarily standard treatment.

Crushing hopes
Hydroxychloroquine was the hottest potential covid-19 treatment a few months ago. While people clamoured for randomised controlled trials, it was dished out liberally to patients the world over. Geleris and colleagues’ observational study in New York City is still not the evidence that can really be acted on. However, it is interesting that in 1446 consecutive patients hospitalised with covid-19, those who received the drug died or were intubated no less frequently than those who did not receive the drug.

As with all observational data, it is important to caution that confounders can explain the relationship or lack of one between an intervention and an outcome. For example, patients who received hydroxychloroquine were more likely to be sicker and therefore do badly, which could have reduced the chance of demonstrating that hydroxychloroquine has a benefit if indeed there is one. I can’t help but agree with the authors’ comments: “Given the observational design and the relatively wide confidence interval, the study should not be taken to rule out either benefit or harm of hydroxychloroquine treatment. However, our findings do not support the use of hydroxychloroquine at present, outside randomized clinical trials testing its efficacy.”

Alex Nowbar is a clinical research fellow at Imperial College London
**COVID-19 REVIEWS**

Richard Lehman

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**Unclean**

The oldest form of protection from infectious disease is to keep infected people away. Old Testament lepers are the best known example. Distancing rules for covid-19 struck me as bizarre from the start, and lack of quarantine as even more so.

How can an arbitrary distance of 2 metres apply across the board, from people sitting inside a restaurant to those in the open air following behind a panting cyclist? (J Infect Dis doi:10.1093/infdis/jiaa189). How come that, until now, people could get off planes from epidemic areas and be left to roam the country at will? Why, when it has been known since February that infected people can shed virus for up to three weeks following onset of symptoms, can they go back to work seven days from the onset of illness?

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**Lovely models available**

I have cultivated a flippancy about models of covid-19, languidly waving them aside like Oscar Wilde with his leg over the arm of a chair. “Ah, you bring me another model! Did you make it yourself? How thoughtful. Leave it on the table by the gardenia, dear fellow.”

Sadly this is a pose which I’ve been forced to give up by academic obligation. Public policy about covid-19 has depended on the mathematical modelling of spread and of the likely effect of interventions, taken singly or together. Those of us who are bad at sums need guidance from critically aware mathematicians about their assumptions and the scale of their uncertainty.

Unfortunately, almost all the evidence we have about interventions comes as bundles of elements adopted at varying times by different countries. Evidence about single interventions is only available in the rare cases where they have been omitted from natural experiments in some populations. **Moral: All models are wrong, but modellers should be able to tell us the bounds of their wrongness**

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**No place like home?**

Gather round children, while I tell you about the days when there were few intensive care units and even fewer hospices, and young GPs like myself would care for all sorts of things at home. Myocardial infarction before thrombolitics, terminal cancer before syringe drivers, heart failure with dig and diuretics: it was just you and the district nurse. If we were still in the 1970s, no doubt most people with covid-19 would be looked after in the community, with the odd cylinder of oxygen and bottle of morphine. I spent several fraught weeks in March and April trying to find out what was going on among patients with covid-19 who remained at home. How did they access care and what did it consist of? Was anyone in charge nationally? How big was the need? I still don’t know the answers. The problem may not be of the scale originally feared (except in nursing homes) but it must be there, largely hidden. **Moral: We are weeks into the UK epidemic, but our primary care based NHS seems to have no coordinated plan for home care**

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**Silver lining**

Re-cognition is a cognitive process that GPs in particular need to perform all day long. People can sense right away whether you are trying to align yourself cognitively with them to see things from their point of view, or if you are brushing them aside to assert your own. The first builds trust, and the second distance. Covid-19 shows that all of medicine needs a process of re-cognition to bring it into alignment with what matters to people. Evidence based medicine started off with that intention, but over 25 years it has drifted towards becoming a set of technical rules for randomised controlled trials. The pandemic forces us to look at the actual evidence around us when we have to make important decisions in a hurry. Nobody has got it entirely right, but the UK has come closer than most to getting it entirely wrong. We need to revise the basic principles of diagnostic testing applied to different problems and populations.

This is only part of a re-cognition agenda that is needed: let’s get on with listening properly to the concerns of people, and sharing the work out. **Confucius: If you think in terms of a year, plant a seed; if in terms of 10 years, plant trees; if in terms of 100 years, teach the people**

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Pregabalin and gabapentin for pain

Stephanie Mathieson,1,2 Chung-Wei Christine Lin,1,2 Martin Underwood,3,4 Sam Eldabe5

What are pregabalin and gabapentin?

Pregabalin and gabapentin, collectively gabapentinoids, are primarily anticonvulsant drugs. Over the past decade, they have been increasingly prescribed for pain. They are recommended for neuropathic pain in adults (table 1, bmj.com), but are commonly used off-label for other pain disorders such as low back pain, sciatica, and migraine. Pregabalin was one of the highest selling drugs globally in 2017. In 2018, more than 14 million prescriptions of pregabalin and gabapentin were issued in England. This increase in gabapentinoid prescribing may be driven by a desire to avoid opioid analgesics.

Pregabalin and gabapentin were reclassified as class C drugs in the UK in April 2019 following an increase in the number of deaths caused by gabapentinoid misuse and addiction. Under the UK’s Misuse of Drugs Act, unlawful possession, production, or supply of these drugs is subject to potential punishments and fines. The US Food and Drug Administration has expressed concern over the increasing use of gabapentinoids, mainly when prescribed concurrently with opioid analgesics or benzodiazepines. Others have called to have both drugs classified as a Schedule V controlled substance, the same class as opioids, to regulate their prescription. Gabapentinoids bind to the α2-delta subunit of voltage gated calcium channels, which decreases the release of glutamate, noradrenaline (norepinephrine), and substance P. This is believed to contribute to their anticonvulsant, analgesic, and anxiolytic actions.

How well do they work?

Neuropathic pain

Moderate quality evidence supports the use of gabapentinoids to improve pain in those with post-herpetic neuralgia or diabetic peripheral neuropathy compared with placebo, as in Cochrane reviews. Nearly four out of 10 people taking pregabalin (600 mg/day) and three out of 10 people taking gabapentin (1200 mg/day) for eight weeks or longer achieve at least 50% pain relief. Pain was reduced by one third for 50% of the participants (table 2, bmj.com, fig 1, fig 2). Evidence for other types of neuropathic pain is limited.

Another systematic review of pharmacotherapy for neuropathic pain reports similar effects with gabapentinoids. However, the pooling of treatment effects across all drug dosages may have overestimated the treatment effect, particularly with variations in study quality.

Fibromyalgia

One in 10 patients with moderate to severe fibromyalgia taking pregabalin (300–600 mg daily) experiences a 30–50% reduction in pain over 12 to 26 weeks, based on high quality evidence from a Cochrane review. The evidence for gabapentin in fibromyalgia is unclear because of the small number of trials and very low quality of evidence available.

Other conditions

Systematic reviews have found no treatment benefits of gabapentinoids over placebo in low back pain, sciatica, and spinal stenosis or episodic migraine in adults. Evidence to support the use of pregabalin in acute pain, HIV neuropathy, neuropathic cancer pain, and other forms of neuropathic pain, is insufficient.

WHAT YOU NEED TO KNOW

- Pregabalin and gabapentin can be effective as first line treatment for some people with neuropathic pain such as post-herpetic neuralgia and diabetic peripheral neuropathy
- They are not effective for low back pain, sciatica, spinal stenosis, or episodic migraine, and their off-label use for these conditions is not advised
- Ask patients to report side effects such as dizziness, sleepiness, and gait problems, which may require the drugs to be tapered and stopped

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We sought views of patients continuing on gabapentinoids for chronic pain as well those who actively tapered gabapentinoids at the James Cook University Hospital pain clinic, UK. A few patients commented that regular review of medications is helpful to balance pain relief against side effects and manage the appropriate dose. If the medication is not providing pain relief, doctors must advise how to stop it. A patient who stopped pregabalin for low back pain after five years commented, “It has taken me three weeks to completely come off pregabalin and I feel much better for it. My back pain hasn’t changed much but I’m less drowsy and more able to do my job.” Another patient came off gabapentin for sciatica with help from their doctor after three years. Based on our feedback we have highlighted the adverse effects of these drugs and added information on prescribing these drugs and follow-up.
Pregabalin and gabapentin, collectively gabapentinoids, are primarily anticonvulsant drugs. Over the past decade, they have been increasingly prescribed for pain. They are recommended for neuropathic pain in adults, but are commonly used off-label for other pain disorders such as low back pain, sciatica, and migraine. Pregabalin was one of the highest selling drugs globally in 2017. In 2018, more than 14 million prescriptions of pregabalin and gabapentin were issued in England.

### Gabapentinoids for pain relief

A summary of the evidence for pregabalin and gabapentin

#### Pain reduction

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pregabalin v placebo</th>
<th>Gabapentin v placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate to severe post herpetic neuralgia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 50% pain reduction</td>
<td>410 260 more 150 *** Moderate</td>
<td>320 150 more 170 *** Moderate</td>
</tr>
<tr>
<td><strong>Moderate to severe diabetic peripheral neuropathy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 50% pain reduction</td>
<td>410 130 more 260 Low</td>
<td>380 170 more 210 Moderate</td>
</tr>
<tr>
<td><strong>Fibromyalgia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 50% pain reduction</td>
<td>240 90 more 150 *** High</td>
<td>No data</td>
</tr>
</tbody>
</table>

#### Adverse events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pregabalin v placebo</th>
<th>Gabapentin v placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate to severe neuropathic pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one adverse event</td>
<td>690 120 more 570 *** Moderate</td>
<td>630 140 more 490 *** Moderate</td>
</tr>
<tr>
<td>At least one serious adverse event</td>
<td>34 NO IMPORTANT DIFFERENCE 34 *** High</td>
<td>32 NO IMPORTANT DIFFERENCE 28 *** Moderate</td>
</tr>
<tr>
<td>Misuse</td>
<td>5 5 more 0</td>
<td>11 11 more 0</td>
</tr>
</tbody>
</table>

#### Adverse events in detail

<table>
<thead>
<tr>
<th>Event reported</th>
<th>Pregabalin v placebo</th>
<th>Gabapentin v placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>240 180 more 60 *** Moderate</td>
<td>190 124 more 66 *** Moderate</td>
</tr>
<tr>
<td>Somnolence</td>
<td>170 120 more 50 *** Moderate</td>
<td>140 88 more 52 *** Moderate</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>No data</td>
<td>140 114 more 26 *** Moderate</td>
</tr>
</tbody>
</table>

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How do they compare with other treatments for neuropathic pain?

Tricyclic antidepressants (number needed to treat 3.6, 95% confidence interval 3.0 to 4.4; moderate quality evidence) and serotonin-noradrenaline reuptake inhibitors (NNT 6.4, 95% CI 5.2 to 8.4; high quality evidence) are other first line drugs for neuropathic pain. They have smaller NNTs than gabapentinoids and are likely to be more effective. 2 The evidence on other anticonvulsant drugs such as carbamazepine, lacosamide, and lamotrigine for neuropathic pain is inconclusive. 2

How safe are they?

Adverse events are common and frequently result in discontinuation of the drug. Nearly two in three patients taking these drugs for neuropathic pain experience an adverse event16–17 (fig 1, 2).

Adverse events

Dizziness (19%), somnolence (16%), and gait disturbance (14%) are commonly reported with gabapentin, based on moderate quality evidence from a Cochrane review. 17 More participants on gabapentin (11%) withdrew from studies because of adverse events compared with placebo (8.2%). 17 Dizziness (24%) and somnolence (17%) are also more frequent with pregabalin compared with placebo (6% and 5%, respectively). 18 Ninety one per cent of participants taking pregabalin (600 mg/day) for fibromyalgia experienced one or more adverse events compared with 73% in the placebo group as in a Cochrane review (three studies, 1122 participants). 16 More participants with fibromyalgia taking pregabalin (28%) withdrew from the studies because of experiencing adverse events compared with placebo (11%). 18

Although serious adverse event rates for gabapentinoids are similar to those of placebo in systematic reviews, 16,17 population based studies show the potential for serious harms. An Australian study found a 57.8% (95% CI 30.0% to 91.6%) yearly increase in intentional poisoning and pregabalin related deaths between 2012 and 2017, corresponding with increased pregabalin prescriptions. 20 Opioids, benzodiazepines, and illicit drugs were commonly taken together in those who overdosed on pregabalin. 20 Co-prescription of opioid analgesics can increase the risk of opioid related overdose and death (odds ratio 1.49, 95% CI 1.18 to 1.88). 21

Potential for misuse

There are 11 940 reports of gabapentinoid misuse and dependence from 2004 to 2015 in an international adverse event database, with more than 75% reported since 2012. A survey of 1500 respondents aged 16-59 in the UK found the self-reported lifetime prevalence of gabapentin and pregabalin misuse was 1.1% and 0.5%, respectively. 22 Misuse was defined as any intentional therapeutic use of a drug in an inappropriate way—ie, aside from prescribed doses. 22 Gabapentinoid misuse was higher in people with opioid use disorders: 3-68% with pregabalin and 15-22% with gabapentin. 22 These values may be an underestimate because of the retrospective nature of included studies. Opioid users tend to select gabapentinoids to boost a euphoric high and reduce withdrawal symptoms while producing only a few adverse effects. 23
Discuss with patients the expected side effects and likely pain relief before prescribing. Pregabalin and gabapentin are effective for some types of nerve-related pain, such as after shingles or with diabetes. Your doctor may discuss starting these medicines if you have such pain. About 40% of patients with post-herpetic neuralgia or diabetic peripheral neuropathy find at least a 50% improvement in pain with these drugs when taken daily for eight weeks or longer. You may need to take these drugs for eight weeks before you experience improvement in pain. These drugs are not effective for pain relief other than in these conditions and their use is not advised. Consult your doctor before starting these drugs so they can assess your medications and illness history before prescribing.

How are they given and monitored?

Given the risk of adverse events and potential for misuse, caution is advised in prescribing these drugs. Discuss with patients the expected side effects and likely pain relief before prescribing. Australian, UK, and Canadian guidelines all recommend gabapentinoids as first line treatment for neuropathic pain. They similarly recommend amitriptyline and duloxetine (Australia and UK) or serotonin-noradrenaline (norepinephrine) reuptake inhibitors (Canada). Use of these drugs for non-neuropathic pain is not advised. No evidence is available for combination pharmacotherapy.

In practice, a trial of the drug for six to eight weeks may be needed to find out if the benefits justify the potential harms. Review the patient’s ongoing medications. Drug interactions are uncommon as in manufacturers’ information, but co-prescribing with opioids can increase the risk for harms. Manufacturer’s advice is to assess for suicidal behaviour and ideation. Exercise caution when prescribing gabapentinoids for patients with a known history or potential for drug misuse or dependence.

Contraindications include known hypersensitivity to these drugs and reduced renal clearance.

Refer to local formulary for appropriate dosing and indications. Manufacturer recommendations for gabapentinoids suggest titration upward for three to seven days in divided doses, to pain relief or a maximum of 600 mg/day for pregabalin in two daily doses and up to 3600 mg/day for gabapentin in three daily doses. Follow up patients to evaluate response to treatment and any adverse events. Consider stopping if there is no improvement in pain or the patient experiences adverse events which interfere with their work and impair quality of life. The drug should be gradually tapered. Abrupt discontinuation may lead to withdrawal effects such as agitation, dysphoria, and fatigue. Reducing the dose by 50 to 100 mg/day each week for pregabalin and a maximum 300 mg/day each week for gabapentin is likely to be safe.

Key
- 32/100 people with post-herpetic neuralgia will have 50% or greater pain relief with ≥1200 mg/day of gabapentin
- 38/100 people with diabetic peripheral neuropathy will have 50% or greater pain relief with ≥1200 mg/day of gabapentin
- 63% adverse events
- 3.2% serious adverse events
- 1.1% misuse
- Not affected

TIPS FOR PATIENTS
- Pregabalin and gabapentin are effective for some types of nerve-related pain, such as after shingles or with diabetes. Your doctor may discuss starting these medicines if you have such pain
- About 40% of patients with post-herpetic neuralgia or diabetic peripheral neuropathy find at least a 50% improvement in pain with these drugs when taken daily for eight weeks or longer
- You may need to take these drugs for eight weeks before you experience improvement in pain
- These drugs are not effective for pain relief other than in these conditions and their use is not advised
- Consult your doctor before starting these drugs so they can assess your medications and illness history before prescribing
- Nearly two in three patients experience side effects such as dizziness, drowsiness, peripheral oedema, and gait disturbance when taking these drugs
- Report to your doctor if you experience any adverse effects so they can advise regarding modifying the treatment. Do not abruptly stop the drug
- If you are already taking an opioid drug for your pain, taking gabapentin or pregabalin is not recommended. The risk of death is increased if you take both of these drugs. If you are already taking both these drugs, talk to your doctor about tapering and stopping one or both of them.

Fig 2: (Top) 32 in 100 people with moderate to severe post-herpetic neuralgia will have at least 50% pain relief when taking gabapentin at ≥1200 mg/day for eight weeks or longer after initial titration compared with 17 in 100 people taking placebo (moderate quality evidence). (Middle) 38 in 100 people with moderate to severe diabetic peripheral neuropathy will have at least 50% pain relief when taking gabapentin at ≥1200 mg/day for eight weeks or longer after initial titration compared with 21 in 100 people taking placebo (moderate quality evidence). (Bottom) Proportion of people with chronic neuropathic pain taking gabapentin (≥1200 mg/day) who will experience at least one adverse event (63 of 100 people compared with 49 of 100 people taking placebo) (moderate quality evidence), serious adverse event (3.2 of 100 people compared with 2.8 of 100 people taking placebo) (moderate quality evidence) and misuse gabapentin (1.1%)
Interpreting a covid-19 test result

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Across the world there is a clamour for covid-19 testing, with Tedros Adhanom Ghebreyesus, director general of the World Health Organization, encouraging countries to “test, test, test.”1 The availability of the complete genome of covid-19 early in the epidemic facilitated development of tests to detect viral RNA.2 Multiple assays with different gene targets have been developed using reverse transcriptase polymerase chain reaction (RT-PCR).3 These viral RNA tests use samples, usually obtained from the respiratory tract by nasopharyngeal swab, to detect current infections. Serology blood tests to detect antibodies indicating past infection are being developed; these will not be considered in depth in this article.

Testing for covid-19 enables infected individuals to be identified and isolated to reduce spread,4 allows contact tracing for exposed individuals,5 and provides knowledge of regional and national rates of infection to inform public health interventions. However, questions remain on how to apply test results to make optimal decisions about individual patients.

How accurate are test results?

No test gives a 100% accurate result; tests need to be evaluated to determine their sensitivity and specificity, ideally by comparison with a “gold standard.” The lack of such a clear-cut “gold standard” for covid-19 testing makes evaluation of test accuracy challenging.

A systematic review of the accuracy of covid-19 tests reported false negative rates of between 2% and 29% (equating to sensitivity of 71-98%), based on negative RT-PCR tests which were positive on repeat testing.6

In one study, sensitivity of RT-PCR in 205 patients varied, at 93% for broncho-alveolar lavage, 72% for sputum, 63% for nasal swabs, and only 32% for throat swabs.7 Accuracy is also likely to vary depending on stage of disease8 and degree of viral multiplication or clearance.9

The lack of a clear-cut “gold standard” is a challenge for evaluating covid-19 tests; pragmatically, clinical adjudication may be the best available “gold standard,” based on repeat swabs, history, and contact with patients known to have covid-19, chest radiographs, and computed tomography scans. Inevitably this introduces some incorporation bias, where the test being evaluated forms part of the reference standard, and this would tend to inflate the measured sensitivity of these tests.11 Disease prevalence can also affect estimates of accuracy: tests developed and evaluated in populations with high prevalence (eg, secondary care) may have lower sensitivity when applied in a lower prevalence setting (eg, primary care).11

One community based study of 4653 close contacts of patients with covid-19 tested RT-PCR throat swabs every 48 hours during a 14 day quarantine period. Of 129 eventually diagnosed with covid-19 by RT-PCR, 92 (71.3%) had a positive test on the first throat swab, equating to a sensitivity of 71% in this lower prevalence, community setting.12

Further evidence and independent validation of covid-19 tests are needed.13 As current studies show marked variation and are likely to overestimate sensitivity, we will use the lower end of current estimates from systematic reviews, with the approximate numbers of 70% for sensitivity and 95% for specificity for illustrative purposes.
What do clinicians need to know to understand a test result?

Sensitivity is the proportion of patients with disease who have a positive test, or the true positive rate. Specificity is the proportion of patients without disease who have a negative test, or true negative rate. These terms describe the operating characteristics of a test and can be used to gauge the credibility of a test result. Sensitivity and specificity can be combined to calculate likelihood ratios, which are dimensionless numbers that indicate the strength of a positive or negative test result (see supplementary file, bmj.com). 15

For calculating probabilities, a likelihood ratio can be used as a multiplier to convert pre-test odds to post-test odds. In the case of the nasopharyngeal swab RNA test for covid-19, the positive likelihood ratio is about 14, which is excellent. 6 A positive covid-19 test result should be very compelling. The negative likelihood ratio is 0.3, which is a moderate result, but not nearly as compelling as a positive result because of the moderate sensitivity (about 70%) of the covid-19 test.

Interpretation of a test result depends not only on the characteristics of the test itself but also on the pre-test probability of disease. Clinicians use a heuristic (a learned mental shortcut) called anchoring and adjusting to settle on a pre-test probability (called the anchor). They then adjust this probability based on additional information. This heuristic is a useful shortcut but comes with the potential for bias. When people fail to estimate the pre-test probability and only respond to a piece of new information, they commit a fallacy called base-rate neglect.

Another fallacy called anchoring is failing adequately to adjust one’s probability estimate, given the strength of new information. Likelihood ratios can give a clinician an idea of how much to adjust their probability estimates. Clinicians intuitively use anchoring and adjusting thoughtfully to estimate pre-test and post-test probabilities unconsciously in everyday clinical practice. However, faced with a new and unfamiliar disease such as covid-19, mental shortcuts can be uncertain and unreliable and public narrative about the definitive nature of testing can skew perceptions.

Fig 1 shows how a clinician’s thinking about a patient’s probability should shift, based on either a positive or negative test result for covid-19. First, the clinician should estimate a pre-test probability, using knowledge of local rates of covid-19 infection from national and regional data and patients’ symptoms and signs, likelihood of alternative diagnoses, and history of exposure to covid-19. After choosing a pre-test probability on the x axis, one should then trace up to either the upper curve for a positive test result or the lower curve for a negative test result, then trace over to the y axis to read the estimate for post-test probability. The figure shows that the shift in the probability is asymmetric, with a positive test result having a greater impact than a negative test result, owing to the modest sensitivity and negative likelihood ratio of the RNA test.

The infographic (fig 2) shows the outcomes when 100 people with a pre-test probability of 80% are tested for covid-19 using natural frequencies, which are generally easier to understand. Online calculators are available which allow clinicians to adjust pre-test probability, sensitivity, and specificity to estimate post-test probability.

What else should clinicians consider when interpreting test results?

A single negative test result may not be informative if the pre-test probability is high

A 52 year old general practitioner in London develops a cough, intermittent fever, and malaise. On day 2 of his illness he receives a nasopharyngeal swab test for covid-19, which is reported as negative. His cough and low grade fever persist but he feels systemically well enough to return to work. What should he do?

Pre-test probability is high in someone with typical symptoms of covid-19, an occupational risk of exposure, and working in a high prevalence region, and negative test results can therefore be misleading. Table 1 (bmj.com) shows that for a pre-test probability of 90%, someone with a negative test has a 74% chance of having covid-19; with two negative tests this risk is still around 47%. If this doctor were to return to work and subsequently the test was confirmed as a false negative, then the decision to work would potentially have significant consequences for his patients, colleagues, and everyone with whom he came into contact. It is therefore safest for this GP with strongly suggestive symptoms to self-isolate in line with guidelines for covid-19, even though his test results are negative. In general, during this pandemic, pre-test probabilities of covid-19 will be high, particularly in high prevalence secondary care settings.

It is safest for a GP with strongly suggestive symptoms to self-isolate even though the test results are negative.
A possible alternative diagnosis will reduce the pre-test probability
A 73 year old woman with severe chronic obstructive pulmonary
disease (COPD) and a chronic cough develops acute shortness
of breath and slight worsening of her non-productive cough.
She reports no fever, has no known exposure to covid-19, and
no recent travel. She presents to an emergency department
where she is acutely short of breath. A chest radiograph shows
possible infiltrates in the right upper and middle lung fields. She
is admitted and placed in isolation on droplet precautions. She
requires intubation for worsening respiratory distress. Initial
nasopharyngeal covid-19 testing is negative. Should she remain
in isolation on droplet precautions?

This patient has an alternative possible diagnosis: community acquired pneumonia. Given her lack of other risk
factors or clinical symptoms, and chest radiography findings we
therefore estimate her pre-test probability at about 50%. One
negative test reduces this risk to 24%, the patient therefore has
an additional independently sampled nasopharyngeal swab
RNA test which was negative, giving a post-test probability
after two negative tests of less than 10%. She is treated with
antibiotics and continues to recover.

What are the implications for practice and
policy?

While positive tests for covid-19 are clinically useful, negative
tests need to be interpreted with caution, taking into account
the pre-test probability of disease. This has important
implications for clinicians interpreting tests and policy makers
designing diagnostic algorithms for covid-19. False negatives
carry substantial risks; patients may be moved into non-
covid-19 wards leading to spread of hospital acquired covid-19
infection, carers could spread infection to vulnerable
dependants, and healthcare workers risk spreading covid-
19 to multiple vulnerable individuals. Clear evidence based
guidelines on repeat testing are needed, to reduce the risk of
false negatives.

Clinicians should ensure that patients are counselled
about the limitations of tests. Patients with a single negative
test but strongly suggestive symptoms of covid-19 should
be advised to self-isolate in keeping with guidelines for
suspected covid-19.

What is the role of serology tests?

Serology tests, which detect immunoglobulins including
IgG and IgM, are under development, with the aim of
detecting individuals who have had previous infection and
therefore theoretically developed immunity. The time course
and accuracy of serology tests are still under investigation, but
the same principles of incorporating the test result with the
clinical impression applies. False positive serology tests could
cause false reassurance, behaviour change, and disease spread.
If suitable accuracy can be established, the benefits of these
antibody tests include establishing when healthcare workers
are immune, helping to inform decisions about the lifting of
lockdowns, and allowing the population to return to work.

Competing interests: See bmj.com.
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**MINERVA**

**Terson’s syndrome**
A case report in *Practical Neurology* describes a 49 year old woman who, following successful coil embolisation for a right internal carotid artery aneurysm, complained of bilateral central visual loss. Funduscopy showed vitreous haemorrhage, which was confirmed by magnetic resonance imaging. She eventually underwent a bilateral vitrectomy, with partial recovery of her vision. Intra-ocular haemorrhage, whether retinal, subhyaloid, or vitreous, in association with subarachnoid haemorrhage, is known as Terson’s syndrome, and in less severe forms it’s far from rare. The corollary is that the presence of retinal haemorrhage in a patient who has temporarily lost consciousness should suggest aneurysmal rupture (*Pract Neurol* doi:10.1136/practneurol-2019-002326).

**Childhood infections and acute lymphoblastic leukaemia**
Circumstantial evidence points to early exposure to infection as a protective factor against childhood leukaemia. Attendance at day care nurseries, being a member of a large family, or being late in the birth order have all been linked to reduced risk. A case-control study from California shows the same thing (*Am J Epidemiol* doi:10.1093/aje/kwaa062). Although a history of infection during the first year of life had no influence on risk of acute lymphoblastic leukaemia, infections in which at least one medication had been prescribed—presumably an indicator of a more severe infection—were associated with a halving of risk. Frustratingly, there’s no clue about which microorganisms were responsible.

**Scapegoats**
Everybody wants a villain—the Chinese Communist Party say, or the World Health Organization, or slow witted Western political leaders—to blame for the pandemic. An essay in the *Atlantic* takes a more grown-up view by analysing the characteristics of life on planet Earth in the 21st century that made the pandemic possible. Among other things it discusses: high levels of air travel; chronic underfunding of public health; a just-in-time economy that depends on fragile supply chains; social networks that spread misinformation; the devaluation of expertise; the marginalisation of the elderly; and poor health of minorities and indigenous groups (https://www.theatlantic.com/health/archive/2020/04/pandemic-confusing-uncertainty/610819).

**Implementation of research evidence**
It’s generally assumed that strong evidence from high quality clinical trials will lead to change in practice, even if that change is sometimes slow to materialise. But case studies of three orthopaedic trials concerned with treatment of fractures of the humerus, radius, and ankle find that the story is more complicated (*BMJ Qual Saf* doi:10.1136/bmjqs-2019-010056). In two cases, the increase in use of the intervention that the trials showed to be superior coincided not with the publication of the trial results but earlier, when recruitment to the trial began. Despite clear cut results, the third trial failed to influence practice.

**Carbon monoxide poisoning**
Several hundred deaths from carbon monoxide poisoning occur every year in Turkey, predominantly in the winter months. The main cause is poorly ventilated stoves used for cooking and domestic heating. Standard treatment, apart from removing the victim from the source of poisoning, is oxygen at atmospheric pressure given through a non-rebreather mask. A small study suggests that it’s better to use a tight mask to deliver oxygen at continuous positive airway pressure (*Am J Emerg Med* doi:10.1016/j.ajem.2020.04.050). Carboxyhaemoglobin saturations fell faster and carboxyhaemoglobin half life was shorter among those treated with continuous positive airway pressure. Unfortunately, there are no data on clinical outcomes.

**Misophonia**
By analogy with misogyny and misanthropy, misophonia ought to mean hatred of noise. In fact, it’s a recent coinage used to label the phenomenon of strong aversive reactions to sounds originating in other people’s oral or nasal cavities, such as chewing, sniffling, slurping, and lip smacking. A report of a large series of cases seen at a hospital in the Netherlands suggests that misophonia is well on its way to becoming a new psychiatric disorder (*PLoS One* doi:10.1371/journal.pone.0231390). Minerva dislikes people with bad table manners as much as anyone, but she does worry about the creeping medicalisation of quirks of human behaviour.

**Treating depression in people with Parkinson’s disease**
Depression is common in people with Parkinson’s disease and it is often undertreated. Although cognitive behavioural therapy has shown promising results and is preferred by many patients to drug treatment, availability is scarce. A small trial suggests that delivery of this treatment by telephone can be an effective alternative (*Neurology* doi:10.1212/WNL.000000000009292). The intervention, which targeted negative thoughts (eg, “I have no control,” “I am helpless”) and behaviours (eg, social withdrawal, worrying excessively), was given weekly for three months, then monthly. It proved substantially better than usual treatment, and benefits persisted.