education

FROM THE JOURNALS Edited highlights of weekly research reviews

Blood pressure management (tailor's version)

Using genetic, biomarker, and other individual characteristics to come up with a tailor-made treatment plan sounds a bit like, well, going to a tailor, but, looking at healthcare systems right now, most people are lucky if they can find something that's good enough off the peg.

A randomised, double blind, crossover trial set in Sweden explored the potential for personalised therapy in people with grade 1 hypertension at low risk for cardiovascular events. Participants took one of four antihypertensives (lisinopril, candesartan, hydrochlorothiazide, or amlodipine) for a month or longer, then, after a washout period, switched to the next one, and repeated this until they'd taken all four. Blood pressure response varied considerably between participants—overall the researchers found that a personalised approach could reduce average systolic blood pressure by a further 4.4 mm Hg. Although this study suggests a tailor-made approach to blood pressure management could be worthwhile, we don't currently have the tools (other than age and ethnicity) to measure people up.

JAMA doi:10.1001/jama.2023.3322

Targeting vascular inflammation as well as cholesterol

Lipid lowering to prevent cardiovascular events gets a lot of the limelight—but have we been overlooking the role of vascular inflammation, thought to be of similar importance to hyperlipidaemia when it comes to cardiovascular risk?

An analysis of three large multinational studies looked at inflammatory risk using a high sensitivity C reactive protein (CRP) test and cholesterol risk using low density lipoprotein (LDL) levels in people with or at high risk of cardiovascular disease already receiving statins. The authors found that high sensitivity CRP was a better predictor of cerebrovascular events than LDL, suggesting vascular inflammation may be a more important focus than lipids in this group of patients.

Lancet doi:10.1016/S0140-6736(23)00215-5

Earning recovery after myocardial infarction

The inverse care law doesn't seem to get much attention these days, so it's good to see a study looking at whether being a high earner means you're more likely to survive a myocardial infarction than someone on a low income. A cross sectional cohort study looked at people in six countries admitted to hospital for at least one day with a myocardial infarction. They calculated mortality rates at 30 days and one year after adjusting for age, sex, and comorbidities.

Overall, those in the top quintile of income had around a 1-3% lower 30 day mortality rate compared with those in the lowest quintile of income. This difference was even greater at one year (although no difference was found at 30 days or a year in Taiwan). However, income was determined by the patient's postcode rather than individual earnings, meaning the findings may also reflect access and quality of local health services and other confounding factors.

JAMA doi:10.1001/jama.2023.1699

None the wiser

The intervention in this randomised trial involving 40 cardiologists was to be taught five communication skills by an experienced coach that go by the mnemonic WISER (Walk in, sit down and make eye contact; Invite, by asking open questions; Say back, paraphrasing what patients have said to show active listening; Emotion, using empathic communication, including naming emotions; and finally Revisit concerns by inviting questions at the end of the consultation).

Analysis of post-intervention audio recordings found that cardiologists given the WISER training improved in the measures of E and R compared with controls who hadn't received the training—perhaps ER is an easier mnemonic to remember when you spend a lot of time there.

JAMA Intern Med doi:10.1001/jamainternmed.2023.0629

Spike in RSV publications

The *New England Journal of Medicine* published five articles on respiratory syncytial virus (RSV) within a day of each other this month. An editorial describes the two new trials—one of an RSV vaccine given in pregnancy, and one in older adults—as the beginning of the end of the fight against RSV. When the bivalent RSV prefusion F protein-based (RSVpreF) vaccine was given in pregnancy, rates of medically attended severe RSV infection in babies up to 180 days old were lower than in the placebo group (0.5% *v* 1.8%).

In the other study, adults over 60 given the same RSVpreF vaccine also had a reduced rate of symptomatic RSV infections compared with placebo, but at seemingly low absolute rates: 1.19 versus 3.58 cases per 1000 years of observation.

N Engl J Med doi:10.1056/NEJMoa2216480, doi:10.1056/NEJMoa2213836

Tom Nolan, clinical editor, *The BMJ*, London; sessional GP, Surrey

Cite this as: *BMJ* 2023;381:p858

Little evidence supports gabapentinoid use in bipolar disorder or insomnia

The study

Gabapentin and pregabalin in bipolar disorder, anxiety states, and insomnia: systematic review, meta-analysis, and rationale

Hong JSW, Atkinson LZ, Al-Juffali N, et al

Mol Psychiatry 2022;27:1339-49

CPD READING

0.5 HOURS

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Why was this study needed?

Gabapentin and pregabalin (gabapentinoids), used to treat pain, seizures, and generalised anxiety disorder, have side effects including drowsiness and dizziness, which are made worse if the drugs are taken alongside pain relieving opioid medication, such as fentanyl and tramadol. The combination can increase the risk of physical accidents, road traffic incidents, and death. Despite this, about one in five people taking an opioid are also taking a gabapentinoid.

These drugs have been classified as controlled in the UK since 2019. However, at least half of all gabapentinoid prescriptions are for conditions for which they are not recommended by the UK's National Institute for Health and Care Excellence. These include some mental health conditions, such as bipolar disorder and insomnia.

A new study explored existing evidence on the use of gabapentinoids to treat bipolar disorder, anxiety, and insomnia.

What did this study do?

This review included 70 studies of mixed quality, which explored gabapentinoid use in bipolar disorder, anxiety, and insomnia. Most looked at anxiety.

What did it find?

Bipolar disorder

The researchers found four studies on gabapentin, but none on pregabalin. The studies included people with different symptoms and looked at different outcomes (hospital admissions, or changes in symptoms, for example). The researchers were therefore unable to pool the results and could not conclude that gabapentinoids are effective for bipolar disorder.

Anxiety

Forty two studies (most on pregabalin) looked at different types of anxiety disorder. Gabapentinoids were more effective than a placebo in treating some severe anxiety disorders (including generalised anxiety, social anxiety, and post-traumatic stress disorder). Their effect was large in some studies; much less so in others.

Insomnia

Eight studies looked at the effect of gabapentin on sleep outcomes such as sleep time and quality; only one study looked at pregabalin. The results were mixed, but generally suggested that gabapentinoids were not helpful for alcohol related insomnia or general sleep problems.

Side effects

Taking gabapentinoids was associated with drowsiness, dizziness, headaches, fatigue, sleep problems, weight gain, and dry mouth.

Why is this important?

Overall, the study found insufficient evidence to support the use of gabapentinoids in bipolar disorder or insomnia. Moderate evidence suggested that gabapentinoids can help people with some severe anxiety disorders. However, the researchers say that other drugs (which do not have the side effects of gabapentinoids) are already recommended for anxiety disorders.

Gabapentinoids are often prescribed for people who have more than one condition. This includes people who have neuropathic pain (this use is licensed, but use in chronic pain is not recommended) and who also have mental health conditions. Doctors may also be selecting gabapentinoids for the many people with bipolar disorder and anxiety.

The researchers stress that, given their side effects and the lack of evidence in some conditions, gabapentinoids should be used with caution.

What's next?

GPs, psychiatrists, and pain clinics need to know that evidence to support gabapentinoid use for bipolar disorder or insomnia is limited, the researchers say. Moderate evidence supports their use to treat severe anxiety disorders. Members of the research team are now investigating exactly how many prescriptions for these drugs are given for these conditions in the UK.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies.
Further details of other interests, disclaimers, and permissions can be found on bmj.com

Cite this as: *BMJ* 2022;379:o2576

ANALYSIS

Adolescent wellbeing in a digital age

Empowering teenagers and strengthening governance of online media are among the urgent actions required to tackle potential harms of internet use, argue **Louise Holly** and **colleagues**

Today's adolescents are transitioning from childhood to adulthood in an era of rapid digitalisation. Digital media—such as online communication platforms and applications accessed through mobile phones, tablets, and computers—are an important window into the world for adolescents. While levels of digital access and experiences of the digital world vary widely, roughly one in three internet users globally are under the age of 18.[2] Younger people also tend to spend more time online than older generations.[4]

Experiences during adolescence are widely accepted as having both positive and negative consequences for health and wellbeing throughout the lifecourse.[6]

To optimise adolescent wellbeing in this digital age, adolescents must be equipped and empowered to use digital media in ways that foster their immediate and future wellbeing.

Box 1 | Categories of risks that adolescents are exposed to when using digital media[18]

Content risks—Potentially harmful content, including violent or pornographic material; discriminatory, hateful, or extremist information; content that perpetuates harmful body image norms; misinformation or disinformation; or age inappropriate marketing

Contact risks—Adolescent experiences or is targeted by potentially harmful adult contact resulting in harassment; unwanted surveillance; sexual abuse; or ideological persuasion, manipulation, or radicalisation

Conduct risks—Adolescent witnesses, participates in, or is a victim of potentially harmful peer contact, resulting in bullying, hostile communication or peer activity (eg, trolling), sexual harassment, non-consensual messaging, or harmful user communities (eg, self-harming or dangerous online challenges)

Contract risks—Identity theft, fraud, online scams, trafficking for sexual exploitation, gambling, micro-targeting of content, and marketing practices that shape behaviour or purchases

Other cross cutting risks—This category includes privacy violations (interpersonal, institutional, commercial), negative physical and mental health impacts of excessive digital media use, and inequalities and discrimination resulting from levels of access to digital media, algorithmic bias, or predictive analytics

Digital determinants of adolescent wellbeing

Digital transformations—that is, the integration of digital technologies and data analytics into all areas of life—intersect with the social, political, commercial, and environmental determinants of health and wellbeing.[8-11] Recognising the many ways in which our health and wellbeing can be directly and indirectly influenced by digital transformations, a Lancet and Financial Times Commission has called for greater recognition of the digital determinants and action to tackle them.[12]

A framework specifically developed for adolescent wellbeing encompasses five domains: connectedness, positive values, and contribution to society; good health and optimum nutrition; safety and a supportive environment; learning, competence, education, skills, and employability; and agency and resilience.[13] Digital determinants can positively and negatively affect wellbeing across each of these domains.[5]

Digital media can improve adolescents' wellbeing in multiple ways. For example, digitally enabled and data driven health systems can help to reduce health inequities and improve quality of care.[14] Digital healthcare offers opportunities for health professionals to reach adolescents in remote and underserved communities and for adolescents to self-manage and monitor their physical and mental health. Online access to health related information is a major benefit identified by young people.[12]

"Hyperconnectivity" may displace in-person relationships and healthy behaviours such as physical exercise

Digital media platforms can support connectedness by allowing adolescents to sustain relationships with friends and family, make new social connections, pursue their interests, and find support networks.

Adolescents use digital media to build their sense of identity, purpose, and fulfilment, and to contribute to their communities. Both formal and informal learning can be enhanced through digital media as adolescents gain access to unprecedented amounts of information and tools to build their knowledge and skills.

A range of risks can arise through adolescent engagement with digital media (box 1). Some design features of digital media can encourage risk taking and promote unhealthy behaviours. "Hyperconnectivity" through digital media may displace in-person relationships and healthy behaviours such as physical exercise.[17] Better evidence is needed on how these risks could result in physical, mental, or emotional harm in adolescents. Nevertheless, given the potential severity of harm to adolescents' health and wellbeing, pre-emptive action is needed.

KEY MESSAGES

- Digital media play an integral part in many adolescents' transition from childhood to adulthood
- The integration of digital technologies and data analytics into all areas of life can directly and indirectly affect adolescent wellbeing in both positive and negative ways
- Tackling the digital determinants of adolescent wellbeing requires coordinated action to empower adolescents and strengthen governance of digital media
- Health professionals can have an important role in supporting adolescents to use digital media to promote their wellbeing and in encouraging governments to put adolescent wellbeing at the forefront of digital governance

Need for coordinated action

How adolescents navigate the opportunities and risks associated with digital media depends on a wide range of individual level factors, including their digital literacy and their wider social, economic, and political environment.[5] Tackling the digital determinants of adolescent wellbeing therefore requires a whole-of-society approach and action at multiple levels. This includes strengthening governance of digital media; increasing adolescents' agency, literacy, and skills; and building the health sector's capacity to respond to the evolving role of digital media for adolescent wellbeing.

Governance of digital media has fallen behind the pace of technological innovation and the evidence base on how digitalisation can support or harm adolescent wellbeing. Action to strengthen governance, such as legislation at national level or self-regulation by technology companies, is often reactive and taken only after a serious incident, such as the preventable death of an adolescent and ensuing media coverage.[20 21] Box 2 summarises some examples of approaches to protect children and adolescents.

Many of the protective measures being introduced by governments and technology companies place a high burden of responsibility on adolescents and their caregivers to understand and then correctly apply the recommended controls. For example, the detailed terms, conditions, and cookie preference pop-ups that users are now invited to review each time they go online assume unrealistic levels of digital literacy. Other approaches, such as "time spent online" warnings in video games, may be easily ignored.[27]

As well as trying to shift user behaviour, policy makers are increasingly recognising that digital media also need to change to align better with the best interests and rights of children and adolescents.[21] While some countries censor the activities of digital media companies or limit young people's access, others, including Australia, Germany, Singapore, the United Kingdom, and the United States, are pursuing approaches that champion child centred design of digital technologies and seek to protect children and adolescents within the digital world rather than restricting them from it.[28-33]

Empowering adolescents

A holistic interpretation of adolescent wellbeing must be central to all approaches. Protective and regulatory measures alone are insufficient for maximising adolescent wellbeing; their need for connectedness, learning, and agency must also be considered. Consequently, to improve wellbeing governments must make digital environments more adolescent friendly while simultaneously reducing digital divides.

Not all parts of the internet can be made safe, and young people will often find ways around even the tightest guardrails.[34] Adolescents will truly be safe online only when risks are minimised and they can identify and deal with any remaining risks themselves. To confidently enjoy the advantages offered by digital transformations and know what to do if they encounter harmful content or practices, all adolescents must have a comprehensive digital education.

A range of initiatives to increase young people's digital literacy and skills are being implemented by governments and non-governmental organisations, but more systematic, population level education and civic programmes are needed to reduce inequities in digital literacy and opportunities.[36]

Adolescents have a right to participate in decisions that affect their lives, which include decisions pertaining to the digital world.[37] Governments can enhance adolescents' sense of agency by empowering and enfranchising them to participate in the design, use, and governance of digital media and technologies. Besides having a huge stake in the outcomes of governance decisions, adolescents' unique experiences and perspectives are critical for building a digital world fit for its youngest inhabitants.[38]

Health sector's role in optimising adolescents' digital media use

Given the potential for health and wellbeing to be both enhanced and undermined by digital media, the health sector must work with other sectors to ensure that they are designed and used in ways that align with health goals.

Health professionals have a vital role in signposting adolescents and their caregivers to verified sources of online health information and support in the event of risky or harmful digital media use. Health professionals working with adolescents should receive regular training to keep pace with fast changing digital innovations, the different ways that adolescents use digital media, and the positive and negative implications of digital media use for health and wellbeing.

As a result of their experiences working directly with adolescents, health professionals can effectively advocate for stronger, more adolescent centred governance of digital media, and for greater investment in population level digital education programmes. Health professionals are uniquely positioned to monitor and gather evidence on the impact of adolescent digital media use and to push for evidence based policies and programmes.

Improving wellbeing has immediate and long term benefits for adolescents, and these benefits will be passed on to future generations.[39] As the role of digital media in young peoples' lives grows, a holistic and rights respecting approach to promoting their wellbeing both online and offline becomes increasingly necessary to enhance the lives of adolescents and wider society.

Box 2 | Common approaches to protecting children and adolescents online

Age assurance—An umbrella term for approaches that are designed to ensure users of a product or service are a certain age.

Data consent pop-ups and cookies—A system used by most websites for acquiring user consent for data tracking in online advertising.

Artificial intelligence (AI) monitoring—AI is already widely used to detect potentially harmful content (eg, explicit, triggering, violent, abusive, and radicalising content) on social platforms such as Facebook, YouTube, Instagram, and LinkedIn[24]

Discouraging excessive use—For instance, YouTube disabled autoplay for younger users; Google turned off targeted advertising and tracking for minors; and Facebook, Instagram, and TikTok made similar concessions.[25]

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Cite this as: *BMJ* 2023;380:e068279

A living WHO guideline on drugs to prevent covid-19

CPD READING
0.5 HOURS

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Clinical question

What is the role of drugs in preventing covid-19?

Recommendations

The second version of this living guideline reiterates the previous strong recommendation against the use of hydroxychloroquine and includes a new conditional recommendation against the use of tixagevimab-cilgavimab in individuals who do not have covid-19.

Understanding the recommendations

The living network meta-analysis informing this guideline included 12 trials (8379 participants) comparing hydroxychloroquine to standard care/placebo, and one trial (5197 participants) comparing tixagevimab-cilgavimab to standard care/placebo. When moving from evidence to the continued strong recommendation against the use of hydroxychloroquine, the guideline development group (GDG) emphasised additional evidence suggesting no or little effect on mortality and hospital admission, and an increased risk of adverse effects. For the new conditional recommendation against the use of tixagevimab-cilgavimab, the GDG emphasised in vitro evidence reducing the applicability of available trial data. While trial results demonstrated modest reduction in the occurrence of laboratory confirmed symptomatic covid-19, lack of in vitro neutralisation of new SARS-CoV-2 sub-lineages was considered to have rendered these results obsolete.

The creation of a new recommendation on tixagevimab-cilgavimab prophylaxis followed the publication of one clinical trial suggesting potential benefits associated with the prophylactic use of these monoclonal antibodies and the subsequent emergence of in vitro evidence suggesting that these clinical trial data were potentially obsolete.[4] For hydroxychloroquine, correspondence following the initial publication of the guideline justified re-examination of whether new evidence reinforced or contradicted the recommendation against hydroxychloroquine prophylaxis.[5]

READERS NOTE

This is the second version of the living guideline for drugs to prevent covid-19. When citing this article, please consider adding the update number and date of access for clarity.

Prophylactically, hydroxychloroquine has no or little effect on death and hospital admission

The guidance

Hydroxychloroquine

Hydroxychloroquine is an immunomodulator that blocks toll-like receptors reducing dendritic cell activation. It is used to treat rheumatoid arthritis and systemic lupus erythematosus. It has an antiviral effect against many viruses in vitro, including SARS-CoV-2, but a clinically useful antiviral effect has not been shown for any viral infection.

The recommendation was informed by the linked systematic review and network meta-analysis that included 12 trials (8379 participants) randomising participants to hydroxychloroquine or to standard care/placebo.[8-19] The trials included participants from North and South America and Europe who either had a known exposure to a person with SARS-CoV-2 infection or who were considered at risk given their professional occupations (such as healthcare workers). The most recent publication of the linked living network meta-analysis contains an additional trial comparing hydroxychloroquine to active interventions.[3 20]

Recommendation: We recommend against the use of hydroxychloroquine as prophylaxis in individuals who do not have covid-19 (strong recommendation).

Understanding the recommendation

Balance of benefits and harm—Used prophylactically, hydroxychloroquine has no or little effect on death and hospital admission (high certainty) and has no or little effect on laboratory confirmed SARS-CoV-2 infection (high certainty). It increases the risk of adverse effects leading to discontinuation of the drug (high certainty).

Subgroup effects—There were no subgroup effects according to known exposure to a person with SARS-CoV-2 infection or hydroxychloroquine dose regimen; extremely low event rates precluded investigation of subgroup effects for mortality. In the absence of subgroup effects, the GDG assumed similar relative effects across subgroups. Certain subgroups of vulnerable individuals, such as immunocompromised patients, were under-represented in previous hydroxychloroquine prophylaxis trials. However, the GDG maintained its view that, given the existing evidence, it would be extremely unlikely that large numbers of under-represented individuals would consent to participate in future hydroxychloroquine trials, and that these would find that hydroxychloroquine prophylaxis meaningfully reduces mortality reduction even in those subgroups.

Visual summary of recommendation

Population

These recommendations apply only to people with these characteristics:

See an interactive version of this graphic online

http://bit.ly/BMJcoprev

Recommendations

No intervention Strong | Weak — or — **Hydroxychloroquine** Weak | Strong

> We recommend not using hydroxychloroquine to prevent covid-19

Evidence profile

Favours no intervention | No important difference | Favours hydroxychloroquine

	Events per 1000 people			Evidence quality
Mortality	3	No important difference	3	★★★★ High
Admission to hospital	3	No important difference	1	★★★★ High
Lab confirmed SARS-CoV-2	62	No important difference	59	★★★★ High
Adverse events	22	6 fewer	28	★★★★ High

No intervention Strong | **Weak** — or — **Tixagevimab-cilgavimab** Weak | Strong

> We suggest not using tixagevimab-cilgavimab to prevent covid-19

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Values and preferences

Hydroxychloroquine

The panel inferred that almost all well informed patients would not want to receive hydroxychloroquine given there are probably no positive effects and there was a risk of adverse events. The panel did not expect there would be much variation in values and preferences between patients for this intervention

Tixagevimab-cilgavimab

The panel inferred that, in the absence of compelling evidence of clinical effectiveness for the currently circulating SARS-CoV-2 sublineages, the majority of informed individuals would not choose to receive tixagevimab-cilgavimab

Justification

Tixagevimab-cilgavimab

The panel reviewed in vitro evidence reducing the applicability of available trial data; while prophylactic use demonstrated modest reduction in laboratory-confirmed symptomatic covid-19, lack of in vitro neutralisation of new SARS-CoV-2 sub-lineages was considered to have rendered these results obsolete

Conditions for use of treatment

Tixagevimab-cilgavimab

Any prophylactic use of this intervention should be restricted to extremely vulnerable individuals, and patients presenting a sublineage that is neutralised in-vitro.

Typical characteristics of extremely vulnerable individuals include:

- People highly unlikely to mount an immune response following covid-19 vaccination
- People at increased risk of developing severe manifestations of covid-19 because of limited physiological reserve

Values and preferences—Applying the established values and preferences, the GDG inferred that almost all well-informed patients would decline hydroxychloroquine.

Applicability—Regarding special populations, none of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, as for other under-represented subgroups, the GDG had no reason to think that children would respond any differently to prophylactic hydroxychloroquine. There were similar considerations with regards to pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently to other adults. Hydroxychloroquine crosses the placental barrier, and there are concerns that it may lead to retinal damage in neonates.

Resource implications, feasibility, equity, and human rights—Hydroxychloroquine is relatively inexpensive and is widely available, including in low resource settings. Although the cost may be low per patient, the overall cost of delivering a prophylactic intervention on a large scale

may be substantial. Moreover, the GDG raised concerns about diverting hydroxychloroquine stocks away from patients with other conditions for whom this medication is indicated.[21]

Uncertainties—The GDG acknowledged that a strong recommendation against hydroxychloroquine to prevent covid-19 indicates that this area is no longer a research priority and that resources devoted to clinical research should rather be oriented to evaluate more promising prophylactic interventions. The GDG felt that further research was unlikely to be acceptable to under-represented subgroups or that it would uncover a subgroup of patients who would benefit from hydroxychloroquine prophylaxis on the most important outcomes (mortality, admission to hospital, and laboratory confirmed SARS-CoV-2 infection).

Tixagevimab-cilgavimab

Tixagevimab and cilgavimab are a combination (Evusheld, AZD7442) of human monoclonal antibodies that bind to non-overlapping regions for the receptor-binding domain of the SARS-CoV-2 Spike protein. Tixagevimab-cilgavimab is administered as a single intramuscular dose of 300 mg.[22]

The combination of tixagevimab and cilgavimab administered prophylactically as intravenous infusion prevented infection in animal models by ancestral SARS-CoV-2, leading to further interest in its use for this indication in clinical practice. However, animal data for currently circulating variants are unavailable, and evidence from in vitro neutralisation studies shows that for more recent variants (including BA.2.75.2, BQ.1, BQ.1.1, and XBB lineages) the in vitro neutralisation of both antibodies is compromised. The GDG concluded that this in vitro evidence rendered the clinical trial results obsolete.

Recommendation: We suggest not to use tixagevimab-cilgavimab in individuals who do not have covid-19 (conditional recommendation).

Understanding the recommendation—When moving from the evidence to the conditional recommendation against the use of tixagevimab-cilgavimab to prevent covid-19-related outcomes, the GDG emphasised in vitro evidence reducing the applicability of trial data. While clinical trial results suggested prophylactic use of tixagevimab-cilgavimab reduced the occurrence of laboratory confirmed covid-19, the GDG concluded that these modest benefits represented the best-case scenario obtained under lineages of SARS-CoV-2 that have since been replaced. Having concluded that recently emerged in vitro evidence rendered the clinical trial results obsolete, the GDG abstained from rating the certainty of the underlying evidence. A conditional recommendation was made recognising that, while it was extremely unlikely for previous SARS-CoV-2 sub-lineages to re-emerge, it nonetheless remained theoretically possible that former sub-lineages would continue to cause covid-19 in certain regions, and that, assuming that real-time monitoring of the prevalence of SARS-CoV-2 sub-lineages was available, a significant number of extremely vulnerable individuals may choose to receive prophylactic tixagevimab-cilgavimab.

Applicability—While the recommendation applies to all individuals who do not have covid-19, a conditional recommendation implies that a minority may opt to receive this prophylactic intervention. Should this situation arise, all GDG members agreed that any prophylactic use of this intervention should be limited to a minority of patients who may be extremely vulnerable, in settings where prevailing SARS-CoV-2 sub-lineages were the same as the ones that caused covid-19 during the trial. Such patients include those who are highly unlikely to mount an immune response after covid-19 vaccination and who, due to a limited physiological reserve, are at high risk of developing severe manifestations of covid-19.

Balance of benefits and harms—Clinical trial data ultimately did not directly bear on the recommendation because it was considered obsolete.

Values and preferences—The GDG inferred that, in the absence of compelling evidence of clinical effectiveness for the currently circulating SARS-CoV-2 sub-lineages, most informed individuals would not choose to receive tixagevimab-cilgavimab.

Resource implications, feasibility, equity, and human rights—The GDG placed a low value on potential benefits in regions where circulating SARS-CoV-2 sub-lineages demonstrate neutralisation activity, and considered that tixagevimab-cilgavimab is a costly intervention of limited availability and requiring parenteral administration. Conversely, the GDG placed a high value on preserving resources for interventions with a high certainty of benefit and noted the availability of effective therapeutic options for patients with covid-19.

Uncertainties—All members of the GDG acknowledged that the available in vitro data suggests that the results of the published clinical trials are now, at best, highly uncertain. However, the GDG was split regarding the strength of recommendation. This was driven by the certainty with which guideline users could rule out that the prevailing SARS-CoV-2 sub-lineages in their region would be resistant to tixagevimab-cilgavimab neutralisation. Those 14 panelists who voted for a strong recommendation pointed out that emerging sub-lineages tended to rapidly replace older sub-lineages all over the globe and that regional real-time monitoring of circulating SARS-CoV-2 sub-lineages was onerous and unrealistic in most geographical areas. Notwithstanding, those 17 panelists who voted for a conditional recommendation argued that, provided that these conditions could be satisfied, some highly vulnerable patients may choose to receive tixagevimab-cilgavimab.

The GDG inferred that restricting use of tixagevimab-cilgavimab to clinical trials would be futile considering the large number of participants required to demonstrate clinical effectiveness.

Competing interests: See bmj.com.

Cite this as: *BMJ* 2021;372:n526

Find the full version with references at http://dx.doi.org/10.1136/bmj.n526

Some highly vulnerable patients may choose to receive tixagevimab-cilgavimab

WHAT YOUR PATIENT IS THINKING

Help me manage my sickle cell pain

Mary Shaniqua

shares her experience of living with sickle cell disease and the importance of empathy

ROSE LLOYD

CPD READING

0.5 HOURS

WHAT YOU NEED TO KNOW

- Patients bring their own knowledge, instincts, and experience. Hearing these can help you work together
- Finding shared interests or common ground can help patients relax and cultivate a more trusting relationship
- Patients have whole lives outside their health. Ask them about this to gain greater insight into their plight

EDUCATION INTO PRACTICE

- What could you do to help someone navigate the pain they are experiencing?
- How can you ensure you are taking a patient's experience into consideration when managing pain?
- When might you consider asking a patient about their life beyond their health condition?

I received a diagnosis of sickle cell disease when I was around 18 months old. I have since experienced very challenging symptoms and diagnoses, including avascular necrosis, iron overload, and pulmonary embolism. Changes in my body caused by sickle cell have also significantly affected my mobility and my social life.

Experiencing a crisis is awful. The pain is excruciating. It feels like someone armed with knives in their hands and spikes on their feet jumping, stabbing, and stamping to their own rhythm inside a selected part of my body. The knives feel like they are deep within the epicentre of my bones and stabbing outwards, at every angle, in an attempt to escape; creating a piercing radiating pain.

When I present to you in crisis, I am in agony. But you can help me through these difficult, traumatic—yet recurring—vulnerable periods in my life.

Empathy is crucial

When I am experiencing a sickle cell crisis, empathy is crucial. Empathy means recognising that I am suffering, listening to me, and engaging me in decisions about my treatment. It can be as simple as reassuring me that resolving my pain is your priority, even if it means we must take some steps back to move forward.

I remember an admission to hospital when my pain was so excruciating I was frozen to the bed in a seemingly awkward position. I was trying, but failing, to distract myself with a book. The doctor doing the ward round came in and saw my position, and immediately recognised I was in a lot of pain and that we needed to change strategy.

Empathy means recognising that I am suffering, listening to me, and engaging me in decisions

He shifted the conversation briefly to the book, which helped calm me a bit. He then asked me about myself, what I do, and what I was looking forward to on discharge. We found common ground and spoke about our shared interests.

This helped me understand that he truly saw me as a person, and cared about making me better. He suggested going back to a higher dosage of pain relief, which was an apparent step back, but it worked in making me more comfortable.

So much more than my disease

Sickle cell has a huge impact on my life, but I am so much more than a sickle cell patient. There are many components to me that are often lost when I enter a hospital.

My life away from the hospital is beautiful, and I desperately want to get back to that life. Days spent in hospital have wider impacts on my family, career, and social life, and can have adverse consequences for me financially. This is why resolving the sickle cell crisis, as quickly as possible, is my top priority.

My plea to doctors is to show empathy, release any negative preconceptions about how people manage pain, and prioritise resolving the pain so that I can get home as soon as it is safe to do so.

Competing interests: None declared.

Cite this as: *BMJ* 2023;381:p475

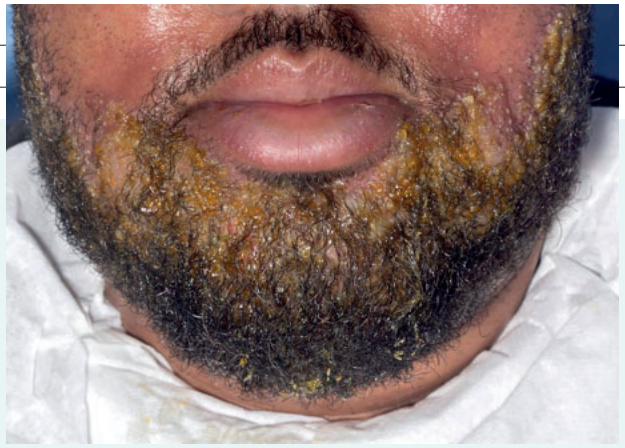
CASE REVIEW

Facial swelling and beard crusting

A man in his 40s presented to the emergency department with a 24 hour history of facial swelling, itching, and oozing after using black henna hair dye on his beard the previous day. He noticed itching five hours after washing it off. His GP had prescribed cetirizine and flucloxacillin, but the patient attended the emergency department the next day as he felt his symptoms were worsening. He was usually fit and well and did not take regular medications. He was allergic to seafood and had had a previous reaction to artificial henna hair dye.

On examination he had tight bilateral facial swelling extending from the top of his beard to beneath the lower border of the mandible. His mouth opening was limited to 1.5-2 cm, and golden crusting and pustules were present throughout his beard (figure). He displayed no signs of respiratory distress and had normal tongue mobility with no airway concerns. No obvious areas of fluctuance or dental pathology were noted on examination.

His temperature was 38.1°C, heart rate 107 beats/min, and respiration rate 20 breaths/min. His white cell count was 16.55×10^9/L (normal range $4.0\text{-}11.0\times10^9$/L), and his C reactive protein level was 71 mg/L (normal range <10 mg/L).



Clinical appearance of the patient on presentation to the hospital. Golden crusting and background erythema limited to the beard area is visible, as is lip swelling and loss of natural lip creases

1 What are the differential diagnoses?
2 What is the most likely diagnosis?
3 How would you manage this patient?

Submitted by Lucy Charles, Sophina Mahmood, and David Sutton

Patient consent obtained.

Cite this as: *BMJ* 2023;380:e072331

answers

CASE REVIEW **Facial swelling and beard crusting**

1 What are the differential diagnoses?

Differential diagnoses include allergic contact dermatitis secondary to the hair dye, facial superficial skin infection, and Ludwig's angina. Ludwig's angina is bilateral cellulitis of the floor of the mouth and should always be considered with bilateral swelling of submandibular and submental regions. Lack of causative dental pathology, fluctuance, and airway compromise and the preservation of normal tongue mobility with soft floor of mouth contribute to the exclusion of this diagnosis.

2 What is the most likely diagnosis?

Acute allergic contact dermatitis secondary to paraphenylenediamine (PPD), probably with a superimposed skin infection. PPD is a chemical commonly found in hair dyes and may be added to natural henna to make it black. The prevalence of allergic contact dermatitis from PPD is reported to be up to 1.5%, but this is thought to be an underestimation. The use of PPD in artificial henna is unregulated, and concentrations can vary considerably. Individuals who have used black henna previously can be sensitised to PPD, and repeat exposure can cause allergic contact dermatitis ranging from mild itching to severe eczema, occasionally with erythema multiforme-type dermatitis. The golden crusting suggests a superimposed secondary infection with either a streptococcus or staphylococcus.

3 How would you manage this patient?

Treat allergic contact dermatitis with topical or systemic corticosteroids. Antihistamines do not significantly help in the treatment of PPD allergic contact dermatitis since it is a type IV hypersensitivity reaction, rather than a type I (IgE mediated) hypersensitivity in which antihistamines play a larger role.

Sensitisation to PPD is dependent on time and dose of exposure, so it is advised to limit contact between the skin and hair being dyed. This is more challenging for facial hair or hair near the scalp.

Antimicrobials active against both *Streptococcus pyogenes* and *Staphylococcus aureus* should be used initially to treat skin infections since clinical differentiation between staphylococcal and streptococcal infections is unreliable. Flucloxacillin is recommended as the first line treatment, but care must be taken to ensure the organism is not resistant. Culture and sensitivity testing should be carried out, ideally before giving any antibiotics.

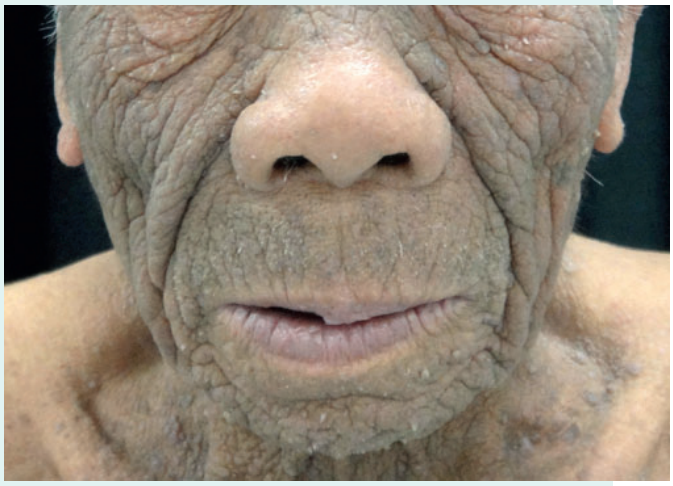
LEARNING POINTS

- Artificial henna contains paraphenylenediamine (PPD), a known contact allergen that can cause an allergic reaction
- Treatment for allergic contact dermatitis includes corticosteroids, and antihistamines have limited use
- Start empirical treatment to prevent deterioration, but recognise the importance of a holistic approach and multidisciplinary care in acute cases that have an unusual presentation.

PATIENT OUTCOME

See bmj.com.

Thick skin with a sinister cause



This is malignant acanthosis nigricans in a man in his 80s. He presented with a 10 day history of upper abdominal pain preceded by two months of itchy, thickened, and hyperpigmented lesions on his face, neck, chest, and extensor surfaces of the limbs. On physical examination, diffuse velvety skin lesions and seborrhoeic keratoses were evident. This appearance, known as the Leser-Trelat sign, is characteristic of malignant acanthosis nigricans. Acanthosis nigricans is characterised by velvety, hyperpigmented, papillomatous lesions, usually in skin flexures and associated with obesity or insulin resistance. Rarely, acanthosis nigricans can be associated with internal malignancy. When associated with malignancy, acanthosis nigricans may develop more rapidly than with non-malignant causes, and skin lesions can occur in unusual sites such as the oral cavity, palms, and soles.

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Patient consent obtained.

Cite this as: *BMJ* 2023;381:e073424

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Patients with intellectual disability

People with intellectual disability need extra care when they're admitted to hospital. A study from England using linked clinical datasets raises suspicions that they aren't getting it. Among 2500 admissions of people with intellectual disability, less than 3% had the condition accurately noted in their hospital records. Even when the criteria were relaxed to include the broader label of learning difficulty, only a quarter had the condition recorded (*PLoS Med* doi:10.1371/journal.pmed.1004117).

How many steps a day?

Ten years' follow-up of 3000 adults who had worn an accelerometer in 2005 found that all cause mortality was 15% lower among those who had taken more than 8000 steps on one or two days during the week of accelerometer recording when compared with people who had never reached that threshold. Surprisingly, walking 8000 steps on more than two days a week didn't seem to be associated with any additional benefit (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2023.5174).

Effects of exercise on cognition

Numerous observational studies, like the one described above, have shown associations between physical activity and better health outcomes. Whether this relation is causal isn't clear. Randomised trials might provide an answer, and an umbrella review of trials of the effects of exercise on cognitive function concludes that any benefits are small. What's more, the benefits become smaller still after accounting for baseline differences, and disappear entirely after correcting for publication bias (*Nat Hum Behav* doi:10.1038/s41562-023-01554-4).

Diagnosing cellulitis

A meta-analysis reveals that a diagnosis of cellulitis frequently needs revision. Among 900 patients admitted to hospital with a label of cellulitis, more than a third were later given a different diagnosis. The commonest alternative diagnoses were non-infectious, with venous stasis being the most frequent. Alternative diagnoses involving infection included abscess, septic bursitis, and osteomyelitis (*J Hosp Med* doi:10.1002/jhm.12977).

Basilar artery occlusion

Outcomes after basilar artery occlusion are poor, according to analysis of data from 4000 patients in the US. More than a third of people with the condition died in hospital, and fewer than one in 10 survived to be discharged home without needing services. Around 36% were treated with endovascular thrombectomy, which slightly improved the chances of a favourable functional outcome, but had no effect on mortality (*Ann Neurol* doi:10.1002/ana.26640).

Among 2500 admissions of people with intellectual disability, less than 3% had the condition accurately noted in hospital records

Depression and stroke

An international case-control study (32 countries, 26 877 participants) of survivors of a first stroke identifies depressive symptoms as a weak risk factor. Pre-stroke depressive symptoms were associated with a small increase in the odds of both intracerebral haemorrhage and ischaemic stroke. Depressive symptoms before admission were also linked with a poorer functional outcome (*Neurology* doi:10.1212/WNL.0000000000207093).

Sexism in science

Nancy Hopkins, a molecular biologist working at the Massachusetts Institute of Technology, thought it unjust that her male colleagues should have the lion's share of the laboratory facilities (*Nature* doi:10.1038/d41586-023-00887-4). One evening in 1993, she used a tape measure to quantify the differences in the amount of space allocated to women and men. MIT was forced to acknowledge that it had been discriminating against female members of its science faculty for years. The tape measure is now in the MIT museum, but the problem persists. A report earlier this year from the Scripps Institution of Oceanography admits that its female scientists had only half as much research space as their male counterparts (*Science* doi:10.1126/science.adg8170).

Cite this as: *BMJ* 2023;381:p828