education

FROM THE JOURNALS Edited highlights of weekly research reviews

What does long covid look like in children?

An estimated 65 million people worldwide may be affected by long covid, some with very debilitating effects. This includes large numbers of school-aged children (6-11 years old) and adolescents (12-17 years), and the presentation isn't necessarily the same as in adults.

This US observational meta-cohort study (RECOVER-Pediatrics) identified 14 symptoms among 5367 school-aged children and adolescents that were more common in those with a history of acute covid infection compared with those who hadn't been infected. There were also four symptoms in school-aged children only and three in adolescents only, which highlights the need to treat the two age groups separately. Overall, high percentages of children and adolescents reported at least one prolonged symptom whether infected or uninfected (45% *v* 33% and 39% *v* 27%). The study developed a research index that will help researchers identify those children likely to have long covid.

JAMA doi:10.1001/jama.2024.12747

Reducing mortality in under 5s

One in 10 children in sub-Saharan Africa die before their fifth birthday, largely due to infectious disease, prematurity, and birth complications.

The AVENIR study conducted in more than 380 000 children in 4272 communities in Niger compared distribution of twice-yearly azithromycin to 1-59 month old children, twice-yearly azithromycin to 1-11 month old infants (the WHO recommendation, to reduce antimicrobial resistance) and then placebo for children 12-59 months old, or placebo only for children 1-59 months old. Mortality was lowest when azithromycin was given during 1-59 months (14% lower mortality compared with placebo), while mortality among infants given azithromycin for 1-11 months only was not significantly lower (6% lower compared with placebo).

N Engl J Med doi:10.1056/NEJMoa2312093

Pelvic floor yoga for urinary incontinence

Pelvic floor yoga has been recommended as a complementary treatment for urinary incontinence (UI), but it lacks a firm evidence base. This Californian randomised trial of 240 women aged 45-90 years reporting daily urge, stress, or mixed type UI compared a 12-week programme of twice weekly group instruction and weekly self directed pelvis floor Hatha yoga (pelvic yoga) with an equivalent length programme of general muscle stretching and strengthening exercises (physical conditioning). The women kept tabs on progress with three-day voiding diaries.

The mean baseline UI frequency of 3.4 episodes/day at outset fell by 2.3 episodes/day with pelvic yoga and 1.9 episodes/day with physical conditioning, with similar improvements whether stress or urge symptoms predominated.

Ann Intern Med doi:10.7326/M23-3051

Media hype for semaglutide

Semaglutide: is there any ill for which it's not being championed? Thankfully, despite the hype, serious research is exploring the scope and limitations of this anti-diabetes glucagon-like (GLP-1 receptor agonist) drug. Heart failure with preserved (or slightly impaired) ejection fraction (HFpEF) is the commonest type of heart failure and often leads to hospital admission and death, especially in overweight or diabetic people. Previous studies found that semaglutide improved symptoms, and this new study used pooled results of four randomised trials to examine whether the drug also reduced progression and death from heart failure.

Semaglutide had no significant effect compared with placebo on cardiovascular events alone (3.1% *v* 3.7%), but it did reduce the risk of worsening heart failure events (2.8% *v* 4.7%) with no additional safety concerns.

Lancet doi:10.1016/S0140-6736(24)01643-X

Trumping the politicians

Termination of pregnancy is a highly politicised topic in the US. Between 2020 and 2023, the proportion of non-hospital abortions in the US that were medical (using mifepristone and misoprostol) rather than surgical increased from 53% to 63%, probably because of covid and the US supreme court decision which eliminated federal protection for abortion.

This prospective cohort study of 510 medication abortions provided through mail-order pharmacy dispensing after an in-person eligibility screening, resulted in 97.8% complete abortions, 91.2% patient satisfaction, and few serious adverse events (0.6%). This is further evidence to support the FDA decision to remove the requirement for in-person dispensing of mifepristone.

JAMA Intern Med doi:10.1001/jamainternmed.2024.1476

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Chronic cough in preschool aged children

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This is part of a series of occasional articles on common problems in primary care. *The BMJ* welcomes contributions from GPs.

CPD READING
0.5 HOURS

A 20 month old boy is brought for review in general practice because his parents are concerned that he has had a persistent cough for nearly six months. Six weeks ago, he was diagnosed with a lower respiratory tract infection based on crepitations heard on auscultation. He was given a five day course of amoxicillin and his cough improved slightly, but only for a few days. A subsequent trial of inhaled salbutamol was ineffective. A week ago, he presented to the emergency department by ambulance as his parents were concerned about noisy breathing and cough. He was given dexamethasone for a clinical diagnosis of croup and discharged later that day.

His parents expect him to have frequent viral infections as he attends nursery, but report that the cough continues even when he is well. He is fully vaccinated, appears to be thriving, and is very active. His development is normal. On examination, he is coughing and appears coryzal. He is afebrile and chest examination is normal, apart from rattly transmitted upper airway sounds. He has had no investigations for his cough to date.

Cough is a common reason for preschool children to be seen in primary or ambulatory care. Estimated prevalence ranges from 5% to 23% of all primary care encounters.[1] Although causes of cough are usually self-limiting, healthcare professionals need to consider and exclude potentially serious underlying conditions. This article outlines how to assess young children with chronic or recurrent episodes of cough and how to make evidence informed management plans with parents.

WHAT YOU NEED TO KNOW

- Chronic cough in preschool aged children is a common cause of concern for parents and caregivers, and has a substantial impact on quality of life for the whole family
- Assess whether the cough is dry or wet, and what triggers are present, to help determine the cause and whether further intervention is required
- For a well child with normal examination findings and no red flag features, no further investigations are required

What you should cover

History

Ask about:

- The nature of the cough: is it wet or dry? The difference can be reliably identified by both clinicians and parents[2]
- Duration of symptoms
- Frequency of coughing
- Change over time, for example diurnal or seasonal variation
- Associated symptoms, such as stridor, wheeze, fever, nasal congestion, choking, or vomiting
- Birth and neonatal period, growth, developmental progress, and feeding history
- Recent exposure to family members or other contacts with symptoms, environmental factors (tobacco smoke, vaping, or aeroallergens), or known triggers
- Immunisation history
- Presence of any "red flag" features (table 1).

What you should do

Examination

- Observe the child's general appearance and document temperature.
- Assess heart rate and respiratory rate against age appropriate values.
- Assess for cervical lymphadenopathy and finger clubbing.
- Inspect the nose for signs of congestion, discharge, or polyps.
- Assess for signs of acute or chronic increased work of breathing, such as intercostal or subcostal recession, tracheal tug, or chest shape changes such as Harrison's sulci.
- Listen to lung sounds and assess for asymmetric air entry, wheeze, or crackles.
- Consider percussion and vocal resonance if there is asymmetry of examination findings.
- Measure the child's weight and length or height, and plot on a growth chart in the child's health record.

Table 1 | Red flag features on history and examination and potential implications

Red flag	Potential implications or cause
Abnormal cry or voice	Laryngeal disorder
Faltering growth	Excessive energy requirements owing to underlying disease process
Family history of chronic lung diseases in childhood	Inherited lung disorder
Fatigue	Chronic disease, malignancy
Finger clubbing	Underlying lung disease, eg, bronchiectasis
Haemoptysis	Infection, foreign body, or vascular anomaly
Nasal polyps	Allergic rhinitis, cystic fibrosis
Onset of cough in the neonatal period	Congenital anomaly, inherited lung disorder
Recurrent coughing during feeds	Palate or laryngeal disorder, swallow incoordination
Sudden onset of severe cough	Inhalation of foreign body
Weight loss or new night sweats	Tuberculosis, malignancy

Table 2 | Differential diagnoses of chronic cough

Diagnosis	Indicators
Protracted bacterial bronchitis	Chronic wet cough, systemically well
Post infectious cough	History of infection, dry cough, gradual improvement
Inhaled foreign body	Sudden onset of symptoms, unilateral chest signs
Environmental irritants or allergens	Exposure to tobacco smoke, vaping, aeroallergens, or pollutants; nasal congestion
Asthma	Recurrent episodes of dry cough, multiple triggers, change over time
Pertussis	Characteristic cough
Tuberculosis	Weight loss, recurrent fever, haemoptysis, malaise
Bronchiectasis (including cystic fibrosis, primary ciliary dyskinesia)	Wet, productive cough; faltering growth
Recurrent aspiration	Coughing with feeds
Tracheo- or broncho-malacia/large airway compression	Chronic brassy or barking cough
Mediastinal neoplasm	Weight loss, recurrent fever

Determining a cause

Infectious causes of acute cough in this age group are common, including viral or bacterial upper respiratory tract infection, bronchiolitis, and pneumonia. They are usually associated with typical features in the history and examination. In a systematic review of one randomised controlled trial and four observational studies reporting time to resolution of acute cough in children under 10, cough resolved in 50% of 828 children by day 10, and in 90% by day 25.[3]

A cough persisting for more than four weeks is considered chronic and should prompt consideration of potential underlying causes (table 2).[4] Although cough related to acute infection typically resolves within four weeks, post infectious cough can last considerably longer, for example after infection with respiratory syncytial virus, pertussis, or mycoplasma.[2] The cough is generally dry and improves gradually over time. Tuberculosis should be considered in countries where it is endemic or in groups at higher risk, for example asylum seekers and refugees.[5]

Protracted bacterial bronchitis is a common cause of chronic cough, characterised by an isolated wet or productive cough without signs of another cause, and which usually responds to two weeks' treatment with an appropriate antibiotic.[6 7] An Australian multicentre study across both community and hospital settings reported that 142 of 346 (41%) children newly referred for chronic cough had protracted bacterial bronchitis.[8] Children with protracted bacterial bronchitis may have crackles audible on auscultation but generally appear well, without systemic symptoms. Failure to improve with two weeks of antibiotics should prompt consideration of other diagnoses, such as bronchiectasis.

Recurrent cough describes two or more discrete episodes in a year, with recovery in between. Ask about potential triggers, for example, viral illnesses or exposure to environmental factors such as tobacco smoke, vaping, allergens, or pollutants.

While asthma is uncommon in preschool children, it should be considered when a child has recurrent dry cough with or without wheeze, or when there are multiple triggers to episodes. Habitual cough often has an unusual character and disappears when the child is asleep.

Symptoms such as regurgitation and irritability related to feeding may suggest gastro-oesophageal reflux disease, although cough is an unusual presenting feature in children and infants.[9] If cough is temporally associated with feeds, consider the possibility of poor coordination of swallowing.

Management

In figure 1, we outline a proposed algorithm for management of chronic cough in preschool aged children.

If the child is well, with normal examination findings and no red flag features, reassure the family that no further investigations are required.

- Recognise the significant anxiety and disruption to life that chronic cough can cause. Explain that no evidence suggests a benefit from taking antitussive or mucolytic agents for cough.[10 11]
- Provide safety net advice, for example to seek review if new symptoms appear. If the child is exposed to potential environmental factors contributing to cough, offer advice and signpost families to further information (for example, the Allergy UK website).
- Consider referral to smoking cessation services if indicated.
- Aim to provide continuity if follow-up attendance is required.

If protracted bacterial bronchitis is suspected, evidence from a systematic review of three randomised controlled trials suggests that the initial treatment of choice is a 14 day course of antibiotics, with a number needed to treat for additional beneficial outcome of 3 (95% confidence interval 2 to 4).[12 13]

- Oral amoxicillin and clavulanic acid in combination is often recommended, as commonly implicated pathogens such as *Haemophilus influenzae* may be resistant to amoxicillin alone.[7]
- Alternatively, a macrolide or trimethoprim-sulfamethoxazole may be used when a child has

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

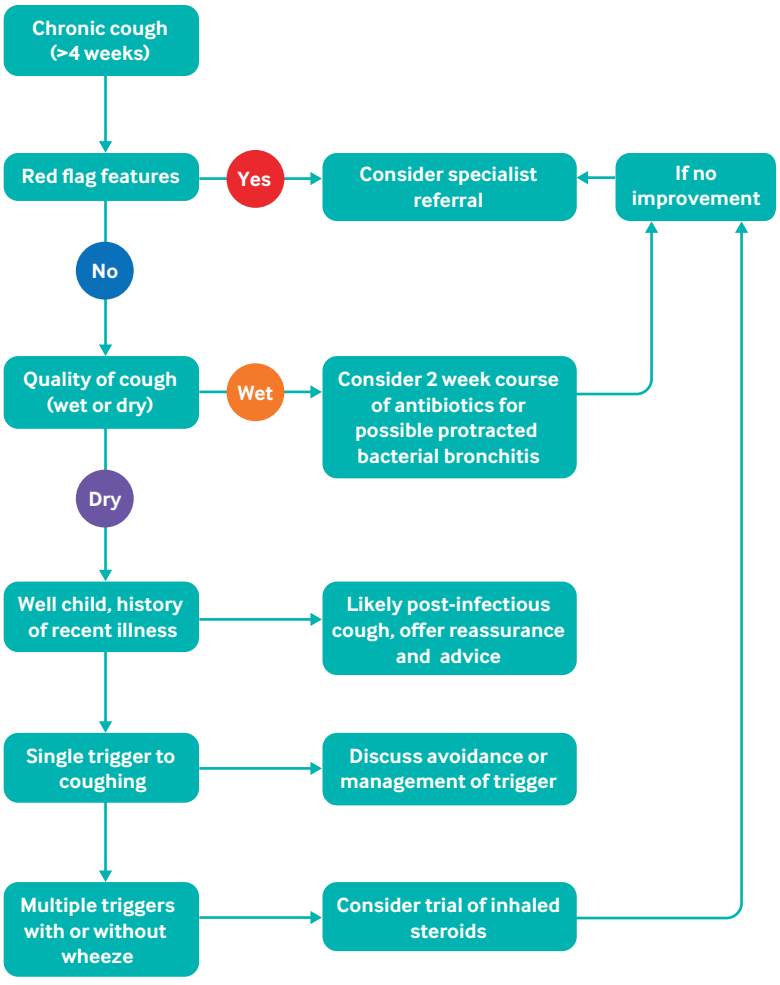
When writing this article, we sought out the experiences of parents and carers of children with cough during assessment in primary care, and during first and follow-up appointments in secondary care. Specifically, the authors asked what most concerned families about their child's cough, what impact the cough had on the family, and what would have improved their experience of the consultation. They discussed what caregivers found helpful and how they felt they might be best supported, and revised the text accordingly. Families particularly wanted to know if, and how quickly, symptoms were likely to improve and what they should do if new symptoms appear.

known penicillin hypersensitivity. Choice of antibiotic should reflect local sensitivity patterns, if known.

If asthma is suspected, for example when recurrent or chronic dry cough is associated with multiple triggers, consider an eight week trial of low dose inhaled corticosteroids, such as beclomethasone[14]:

- Ensure good inhaler technique and review after eight weeks
- Discontinue inhaled steroids if no benefit is seen.

Parents commonly want to know when the cough will go away. Explain that chronic cough in well children usually improves over time, although this can take weeks rather than days, even where treatments are given for possible protracted bacterial bronchitis or asthma. Re-evaluation in person or remotely may be necessary to monitor progress, response to treatment, or to adjust management.



Proposed algorithm for management of chronic cough in children of preschool age

HOW THIS ARTICLE WAS CREATED

This article drew on the experiences of children with chronic cough and their families, as described. The authors discussed common patterns of presentation to primary and secondary care, and how best to identify patients that require further investigation or referral. Guidance from the National Institute for Health and Care Excellence was reviewed, and a literature search was undertaken using relevant MeSH terms and keywords including "cough", "chronic", "persistent", and "child, preschool".

RESOURCES AND SIGNPOSTING FOR CLINICIANS AND PATIENTS/PARENTS AND CARERS

- Royal College of Paediatrics and Child Health. Cough/colds (over 1s). https://www.what0-18.nhs.uk/professionals/gp-primary-care-staff/safety-netting-documents-parents/coughcold-children-1-year-and-over-advice-sheet
- AllergyUK, Allergy resources. https://www.allergyuk.org/resources/
- American Thoracic Society. Patient Education Information Series. Protracted bacterial bronchitis (PBB) in children. https://www.thoracic.org/patients/patient-resources/resources/pbb-in-children.pdf

When to refer

Consider chest radiograph and discussion with a specialist if chronic cough is associated with abnormal findings on examination or fails to improve with initial management. Consider referral to a specialist for further assessment if chronic cough is associated with red flag features. In our practice, we recommend referring children who have more than two episodes of protracted bacterial bronchitis in one year.

Competing interests: See bmj.com.

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EDUCATION INTO PRACTICE

- Think about the last time you reviewed a preschool aged child with chronic cough. Which red flag features did you assess for in the history and examination, and if none were identified, what information did you provide for the family?
- In your clinical practice, review repeat prescriptions for inhaled bronchodilators and inhaled steroids in preschool aged children. Is there evidence of benefit or could a trial without treatment be considered?

STATE OF THE ART REVIEW

New and emerging treatments for major depressive disorder

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Major depressive disorder (MDD) has a substantial personal and socioeconomic impact worldwide. It is a leading cause of disability, affecting 322 million people worldwide and contributes 7.5% of all years lived with disability globally.[1 2] Depression cost the UK about £27.1 billion in 2019, with most costs being attributed to lost productivity.[3] Effective management of MDD is therefore essential to improve the quality of life of people living with the condition. The cause of MDD remains unclear, and MDD is likely not a singular phenotype but a broad and heterogeneous constellation of conditions spanning physiological reactions and pathological states.[5]

Agents that act on monoamine neurotransmission are the mainstay of drug treatment for MDD, but up to 30% of people with a diagnosis of MDD are resistant to traditional drug treatments and considered treatment resistant.[8] No set definition for treatment resistant depression exists, although it is largely viewed as a lack of response to two antidepressants at an adequate dose and duration.[9] One explanation for treatment resistance is that MDD has multiple causes, which has led to the search for novel intervention targets.

This narrative review will focus on novel and emerging treatments for MDD and their effectiveness, safety, and applicability in real world settings.

WHAT YOU NEED TO KNOW

- Much is still unknown about the pathophysiology of major depressive disorder (MDD)
- Treatment resistance highlights the heterogeneous nature of MDD and the need for treatments to target more than monoamine neurotransmission
- New and emerging treatments include drugs such as psychedelics, antibiotics, opioid modulators, neuropeptides, and onabotulinumtoxin; also light based therapies and neuromodulation involving either magnetic or electrical stimulation
- Most research has been conducted on psychedelics, with trials suggesting some promise in the treatment of MDD

Sources and selection criteria

We searched PsycINFO, Medline, EMBASE, and Web of Science using the following search terms: "depression*" AND "novel treatment*" OR "emerging treatment*" OR "innovative treatment*" OR "psychedelics*" OR "neuromodulation.*" Two searches were undertaken; both searches covered a period between January 2017 and June 2023.

Novel treatments

Esketamine and ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist and widely used dissociative anaesthetic that is being increasingly repurposed for use in psychiatry. It is hypothesised that, at sub-anaesthetic doses, ketamine causes an antidepressant effect through glutamatergic modulation.[52] Ketamine has been proposed to facilitate the neuroplasticity involved in new memory formation, fear extinction, and the restructuring of traumatic memories.[53] It is suggested that the psychoactive properties of sub-anaesthetic ketamine doses may facilitate psychotherapeutic processes.[54]

Effects

A single dose of intravenous ketamine appears to reduce suicidal ideation in people with MDD and suicidality[10 55] with effects on suicidality lasting up to five days after dose administration. Trials comparing ketamine with midazolam (as an active placebo) have found significant effects on depression outcomes ranging from less than three days[21] to up to 14 days.[10] Similarly, a Cochrane review of glutamate receptor modulators in the treatment of depression found ketamine to be more effective than placebo, and midazolam specifically, at 24 hours.[11]

Reports of patients developing meaningful insights during dosing sessions, and evidence of possible acute neuroplastic effects, have inspired interest in the possibility of combining ketamine with a psychotherapeutic approach. One trial studied the effectiveness of offering cognitive behavioural therapy (CBT) to participants with treatment-resistant depression who had responded positively to intravenous ketamine infusions,[12] but found no significant difference in depression scores at 14 weeks after infusion compared with treatment as usual.

Intranasal esketamine (the S enantiomer of ketamine) produces a significant and rapid effect within two hours of administration[13-15] with a dose-response relationship.[16]

The most common treatment paradigm in trials is of two applications per week over four weeks. Conclusions vary on the long term effectiveness of esketamine.[13-18]

Side effects and tolerability

In esketamine and ketamine studies common side effects reported include headache (11-27%), nausea (10-16%), vertigo (25%), vomiting (5-18%), dysgeusia (11-27%), somnolence (13-21%), and dissociative symptoms (23-59%).[13 16 19-22] Intravenous ketamine may be more tolerable than electroconvulsive therapy.[21 22]

Clinical application of esketamine and ketamine

Ketamine and its enantiomers seem to show some promise in the treatment of MDD. Intravenous ketamine, most often delivered as one or two 40-minute infusions per week over several weeks, is already in use in many healthcare systems, including the NHS, as an off-licence alternative to electroconvulsive therapy for treatment of severe or difficult to treat depression. Oral ketamine and intranasal esketamine are easier to administer, but the evidence for an effect beyond the course of treatment is still unclear, and there are concerns about habituation and dependence.[56 57]

Esketamine is licensed in the UK for treatment of MDD but is not approved by the National Institute for Health and Care Excellence (NICE) as it does not meet NICE criteria for cost effectiveness.[58] The US Food and Drug Administration (FDA) approved intranasal esketamine for use as an adjunct to an oral antidepressant in the treatment of MDD in 2019 and suicidal ideation in 2020.[15]

Ketamine-assisted psychotherapy will often include psychologically oriented preparation and follow-up "integration" sessions as well as psychological support during doses. However, there is little evidence at present for this approach.[12 54]

Psilocybin

Psilocybin is a commonly occurring hallucinogenic compound found in certain fungi species. Following intense academic and clinical inquiry in the 1950s and 1960s, further research with psychedelics such as psilocybin was severely restricted by drug scheduling laws.[59] Renewed interest has occurred since the mid-2000s, with growing evidence for their use in psychedelic-assisted therapy for MDD.

Effects

Clinical trials with psilocybin have implemented a model of drug-facilitated psychotherapy, in which the drug is administered to support a process of psychological change within a therapeutic relationship and setting. The emphasis, in most cases, is on preparing and supporting the participant through the experience rather than applying any specific therapeutic framework. Psilocybin is administered orally and given either as a single dose or in two doses at least one week apart.[23-25]

In one randomised controlled trial (RCT), participants were randomly assigned to receive the doses either immediately or after an eight week delay. The immediate treatment group showed rapid decrease in depression scores, with a large effect size that maintained statistical significance during the four week follow-up.

However, the first RCT to compare psilocybin (plus psychological support) with an alternative first-line treatment did not show a significant difference in antidepressant effects between psilocybin and escitalopram at week 6.[26]

Side effects and tolerability

The most reported adverse event is headache of mild to moderate severity.[24 25] Challenging intense emotions such as fear, anxiety, and sadness—a common side effect of psychedelic therapy, especially in the acute phase—are widely hypothesised to be an important part of the therapeutic experience, often as part of an "emotional breakthrough."[61] However, there are concerns over increased suicidality.

Clinical application of psilocybin

Recent trials show some promise for psilocybin with psychological support in the treatment of depression, although follow-up periods have been limited.[62 63] Considering that participants in most trials have two therapists supporting them during sessions, which can last up to 10 hours each, scalability may prove an important barrier to widespread use. Emerging evidence of an increase in suicidality may limit treatment to carefully selected and well supported patient groups. Of note, before full regulatory approval, psilocybin has been afforded special status in some healthcare settings such as Switzerland and Australia, where health authorities have approved its prescription for treatment-resistant depression by specifically authorised psychiatrists. Within the US, psilocybin-facilitated psychotherapy for depression has been given "breakthrough therapy" designation from the FDA.[59]

Ayahuasca and dimethyltryptamine

Ayahuasca is a traditional plant medicine made from the *Banisteriopsis caapi* vine, which contains β-carboline harmala alkaloids, and leaves of the *Psychotria viridis* bush, which contain the hallucinogen dimethyltryptamine (DMT).[64] The harmala alkaloids are monoamine oxidase inhibitors that prevent monoamine oxidase from inactivating DMT.[64] DMT is a serotonin and sigma-1 receptor agonist. The function of sigma-1 receptor is not well understood, but it is hypothesised that the receptors may be involved in the pathophysiology of MDD by acting on dopamine neurotransmission.[64] Observational evidence suggests that ayahuasca may reduce symptoms of depression.[65]

Effects

Building on a prior open label study, which showed rapid antidepressant effects for ayahuasca in treatment-resistant depression,[65] in one RCT with participants with MDD ayahuasca was found to have a significant antidepressant effect compared with placebo, with effect sizes increasing between day 1 and the final follow-up at day 7.[27]

Side effects and tolerability

Ayahuasca is associated with a high incidence of gastrointestinal side effects, and in traditional settings vomiting after a dose is often framed as "purging" and considered to be of therapeutic value.[66] One RCT reported that most participants experienced nausea and 57% vomited.[27]

Clinical application of ayahuasca and DMT

While initial results appear promising, with some interesting neurobiological correlates, there is insufficient high quality evidence to recommend the use of ayahuasca for depression.

Neuromodulation

Transcranial magnetic stimulation (TMS) is a form of neuromodulation that involves the targeted use of magnetic fields primarily to stimulate the dorsolateral prefrontal cortex (DLPFC).[39] Traditionally, the DLPFC is important for executive functioning, particularly task shifting, regulation of attention, planning, and working memory.[69] Latterly, its role in the processing of emotions, particularly in integrating emotion and cognition, has been explored.[70] The DLPFC is thought to attribute valence to emotions (that is, the pleasantness or unpleasantness of an emotion). Reduced activity within this region has been noted in patients with depression.[39-44 71 72]

The standard protocol for repetitive TMS involves magnetic stimulation at 10 Hz being applied 75 times during a session lasting 37.5 minutes, and sessions are undertaken daily for five days over a four to six week period.[73] Repetitive TMS is recommended by NICE in England for the management of severe MDD.[74] Newer forms of TMS identified by our search strategy included accelerated TMS, theta burst stimulation, Stanford neuromodulation therapy, and low field magnetic stimulation.

Accelerated TMS is a form of repetitive TMS in which treatment sessions are delivered multiple times a day, thus shortening the treatment period.[39 43]

Theta burst stimulation (TBS) involves stimulation being applied at a higher frequency than repetitive TMS for up to 3 minutes per treatment session.[44 71] TBS has been trialled as a monotherapy and as an adjunct to traditional antidepressant therapy. Two forms have been studied: continuous TBS involves uninterrupted stimulation while intermittent TBS involves stimulation being applied every few seconds.[42 71]

Stanford neuromodulation therapy is an accelerated form of intermittent TBS involving multiple sessions within a day, and trialled as an adjunctive treatment.[41] Mean reduction in depression score among participants was greatest at week 1 and remained clinically significant at week 4.[41]

A systematic review which compared forms of TMS against the established treatment electroconvulsive therapy stated that bilateral TBS has the potential to be the most efficacious of the 16 neuromodulation procedures assessed for treatment-resistant depression; however, as the comparison was through a network meta-analysis, further direct comparisons are needed.[46]

Side effects and tolerability

Very few serious adverse effects have been reported for any forms of neuromodulation. Headache is most reported, occurring in 64% of participants who underwent repetitive TMS in one study.

Clinical application of newer forms of TMS

Repetitive TMS and its newer protocols appear to be more effective than sham therapy with few adverse effects. However, we found very few studies that compared forms of TMS against other treatments. Although TBS or accelerated TMS may not be more effective than repetitive TMS, both can be administered in a significantly shorter timeframe and are well tolerated.

Emerging treatments

Pharmacological

Anti-inflammatory agents

Neuropeptide Y is involved in the regulation of inflammation and noted to be reduced in people with MDD and other psychiatric disorders.[30 77] An RCT administered neuropeptide Y intranasally as an adjunct to an antidepressant. There was a significant antidepressant effect compared with placebo within 24 hours of administration, but this did not persist at 48 hours. Strong conclusions cannot be made at present due to the limited research.

Minocycline is a tetracycline and is typically administered in capsule form.[78] It has been trialled as a monotherapy and as an adjunct to an antidepressant.[31] In two systematic reviews, minocycline significantly reduced depressive symptoms when compared with a placebo or treatment as usual. Minocycline is well tolerated.[32-34] Early studies may signal its use as an adjunct over monotherapy but further research is needed.

Non-steroidal anti-inflammatory drugs (NSAIDs)—Celecoxib has been trialled as an adjunct to an antidepressant.[31] Meta-analysis of four trials found there to be a significant reduction in depressive symptoms compared with an antidepressant alone.

Statins—RCTs have compared the use of statins as an adjunct to an antidepressant with the antidepressant alone.[31] The addition of a statin is more effective at reducing depressive symptoms than antidepressants alone.

Omega-3 fatty acid has been trialled as a monotherapy or adjunctive to treatment as usual.[31] A significant reduction in depressive symptoms has been found.

Buprenorphine-samidorphan

We found two RCTs trialling a combination of buprenorphine and samidorphan, a weak opioid antagonist, administered daily in the form of a sublingual tablet as an adjunct to an antidepressant.[35] Higher doses of the buprenorphine-samidorphan drug caused

a greater reduction in depressive symptoms compared with the placebo group in both trials. Buprenorphine-samidorphan as an adjunct to established treatments appears to show promise, but conclusions regarding its effect with long term use cannot be made from the current research.

Onabotulinumtoxin A

We identified two articles in which a single injection of onabotulinumtoxin A into the glabellar region was used as either a monotherapy or as an adjunctive treatment to antidepressants.[36 37] A significant antidepressant effect was found compared with placebo. Strong conclusions cannot be made using current research.

Neuromodulation

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) involves weak electrical signals being delivered to a patient's scalp to target the dorsolateral prefrontal cortex.[46 47] Little is known about the effectiveness of tDCS in forms of depression other than vascular depression. A systematic review found it to be non-inferior to sham therapy in more common forms of depression, but there was little other evidence.[46] A combination of tDCS and cognitive behavioural therapy (CBT) does not have a significant antidepressant effect over CBT alone or CBT with sham tDCS.[48]

Light therapies

Bright light therapy entails the use of a light box that patients sit in front of in the morning while it emits light at a controlled wavelength.[49 50] Bright light therapy may have some applicability as an adjunct to repetitive TMS. The US Departments of Veterans Affairs and Defence recommend bright light therapy for people with "mild to moderate MDD, regardless of seasonal pattern or component."[79]

Photobiomodulation is a type of light therapy administered at low levels of red and near infrared light.[51] One trial found a significant decrease in depressive symptoms with photobiomodulation compared with sham therapy.[51]

Most studies report no adverse effects from either photobiomodulation or bright light therapy; one study within the search reported a few cases of mild headaches associated with bright light therapy.[49] Systemic photobiomodulation does not have enough evidence for recommendation for wider use.

Deep brain stimulation

Deep brain stimulation (DBS) is an invasive treatment in which electrodes are surgically implanted into the brain and stimulate electrical activity.[46] A systematic review comparing multiple forms of non-invasive neuromodulation found that DBS was less effective than repetitive TMS.[46] Considering the invasive nature of DBS, it cannot be recommended for wider adoption except in extreme circumstances and only when other interventions for MDD have failed.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We sought feedback from people participating in trials of psychedelic treatments for major depressive disorder on our search strategy, findings, and analysis. One participant provided the following feedback (reproduced with permission):

"Having been struggling with depression for over a decade, I have now been through several different types of treatment and therapies without a lasting success. I have been trying to keep up with the latest developments on the subject of novel therapies, but the myriad of clinical trials and papers on the novel therapies is overwhelming. [This article] brings a timely and much needed review on all the latest results and developments. The authors did an exhaustive search for novel treatments and made a very comprehensive summary of the results obtained with each type of treatment. This review highlights which treatments seem to be the most promising and also raises some of the issues that still need addressing in order for those to become mainstream."

Magnetic seizure therapy

Magnetic seizure therapy (MST) involves the induction of seizures using high-dose magnetic stimulation.[46] It is performed under general anaesthesia.[80] A systematic review found it to be non-inferior to electroconvulsive therapy[46] but with a higher discontinuation rate. Current data are limited, so conclusions on wider adoption are difficult to make at present.

Guidelines

The US Departments of Veterans Affairs and Defence recommends offering ketamine or esketamine to people with MDD who have "not responded to several adequate pharmacologic trials" on the "balance of consistent evidence of benefit weighed against the risks for adverse effects and the limited information on the long term consequences."[79] The guidelines also recommend the use of repetitive TMS in such patients. They considered but did not include psilocybin in their recommendation. The guideline does recommend bright light therapy for people with "mild to moderate MDD, regardless of seasonal pattern or component." Similarly, the European Medical Agency approved the use of ketamine for people with treatment resistant depression in 2019.[81] In contrast, the National Institute for Health and Care Excellence (NICE) in England, did not recommend ketamine or esketamine in the same patient population on the basis of uncertain cost effectiveness[82] (which suggests that, were the cost to reduce in the future, it may be approved). NICE has not made specific recommendations on any of the other interventions we identified, although it noted that evidence of the efficacy of repetitive TMS "in the short term is adequate, although the clinical response is variable;" it makes no specific recommendations for its use.

Competing interests: See bmj.com.

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Shutdown protocols for IT—reducing energy waste in medical practice

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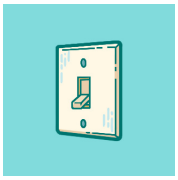
This article is part of a series that offers practical actions clinicians can take to support reaching net zero. Browse all the articles at https://sandpit.bmj.com/graphics/2023/tangibleActions-v8/. To pitch your idea for an article go to https://bit.ly/46Etl9i

CPD READING

0.5 HOURS



Desktop computing has an often overlooked and significant impact on the environmental footprint and financial costs in healthcare, particularly in IT intensive specialties such as radiology. Installation of automatic daily shutdown protocols for computer workstations after core working hours provides a simple and highly effective means to reduce energy waste in everyday practice.

Why change is needed

A US study that assessed the electrical consumption of workstations and monitors in a radiology department found an annual consumption of 138 MWh, the equivalent of driving almost 400 000 miles in an electric car, with an associated financial cost of £12 000.[2] Many areas within hospitals do not require 24/7 computer access—for example, in outpatient departments and administration and management offices.

Evidence for the solution

Studies have shown that changes to protocols on shutting workstations at the end of the work day had significant effects on departmental electrical consumption and carbon footprint. In the UK, Imperial College Healthcare NHS Trust published the results of introducing a new computer power management solution to automatically shut down computers when not in use to reduce energy consumption. This saved the trust £440 000 and reduced its carbon footprint by 590 tonnes within six months of its implementation.[3] Another study showed a reduction of about 45% of the initial IT energy consumption—equivalent to the annual energy use of five households—through configuring reporting stations to automatically shut down after one hour of inactivity.[4]

What you can do

Turning off computers and devices at the end of a working day is a task that may seem simple, but relying on the user to do this is often unsuccessful.[1] Software protocols can be set up on individual computers to selectively turn them off in the evening and back on in the morning, eliminating the need to rely on the final user of the day to turn off their computer. These protocols do not require complex or proprietary software, can be configured using default Windows settings, and allow for pre-shutdown prompts and abort functions to ensure no disruption to workflow. Set up this way, computers can be turned back on whenever needed, and critical infrastructure can easily be exempted, ensuring safety and that only idle devices are switched off.

Medical professionals can work with IT departments to identify which devices these protocols can safely be applied to. Contacting the IT department is the first step in achieving this. Subsequently, identify which computers to target, and which to exempt to ensure there is no disruption to critical IT infrastructure. Next, have a conversation with stakeholders in your department to work out which computers to target and to plan a limited initial rollout (eg, to offices but not clinics), before expanding outwards. This reduces risk and makes the process easier and more manageable.

The impact of your intervention can be assessed simply by looking at average on-time for the selected computers, data your IT department can routinely obtain; alternatively, more in-depth information can be obtained by using watt meters to formally assess energy consumption of plugged-in devices.

WHAT YOU NEED TO KNOW

- Across healthcare settings, desktop computers are often running continuously, whether they are in use or not; this contributes to significant ecological burden and has financial implications
- Automatically shutting down unused IT infrastructure overnight can facilitate significant energy and cost savings, with an associated reduction in greenhouse gas emissions. Shutdown protocols can be installed by local IT teams and are both adjustable and easily aborted to ensure no effect on workflow. Workstations in critical areas or those in use overnight can be exempted from the shutdown protocol installation

EDUCATION INTO PRACTICE

- Which stakeholders in your workplace would need to be involved in a shutdown project, and how could you garner their support?
- What risks would accompany this project in your workplace, and how could you mitigate these?

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Competing interests: None declared

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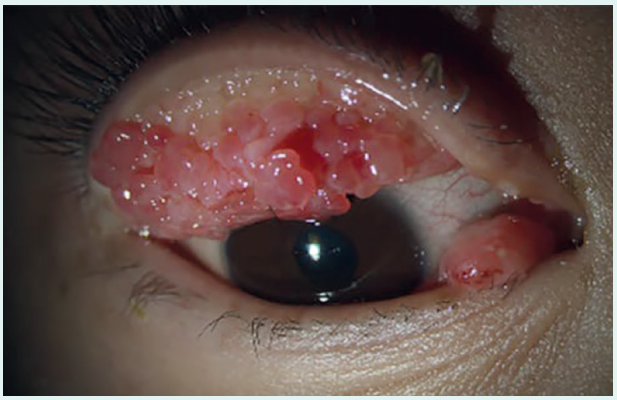
Giant conjunctival papillae

This is vernal keratoconjunctivitis, a chronic, bilateral, and often seasonal allergic inflammation of the conjunctiva characterised by papillae on the inner eyelid and throughout the limbus. The patient, an 11 year old boy, presented with a three month history of itching, irritation, and mucoid discharge from both eyes. His best corrected visual acuity was 6/6 in each eye. Slit lamp examination showed conjunctival congestion alongside large, flat topped, confluent cobblestone papillae across the upper and lower tarsal conjunctiva of both eyes. Notably, a congested papilla extended beyond the right eyelid on the lower tarsal conjunctiva.

Risk factors for this condition include male sex, exposure to dust, residing in a warm and dry climate, and a history of non-ocular allergic diseases. Vernal keratoconjunctivitis can be managed using topical antihistamines, mast cell stabilisers, immunomodulators, and corticosteroids. In instances where giant papillae do not respond adequately to medical treatment, surgical intervention may be considered.



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Parental consent obtained.
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If you would like to write a Minerva picture case, please see our author guidelines at bit.ly/29HCBAL and submit online at bit.ly/29yyGSx

The benefits of social engagement

Social isolation and loneliness have long been linked to increased mortality and functional decline. Data from two longitudinal studies, one in the UK, the other in the US, suggest that interventions to increase social engagement might make a difference. In both studies, high levels of social engagement at baseline were associated with a lower risk of developing frailty. What's more, among older adults who were already pre-frail or frail, increased social engagement was associated with reversal of frailty (*Am J Epidemiol* doi:10.1093/aje/kwae221).

Resveratrol in osteoarthritis

Resveratrol is a naturally occurring polyphenol produced by some plants in response to injury. It is believed to have anti-inflammatory properties, and the benefits of drinking red wine are sometimes attributed to it. Disappointingly, a randomised trial finds that it confers no advantages for people with painful knee osteoarthritis. Participants, mean age 61, were assigned either to 80 mg of oral resveratrol daily or to placebo. At three months, reported knee pain was no less severe in those taking resveratrol (*PLOS Med* doi:10.1371/journal.pmed.1004440).

Olympic sponsorship

The longest standing commercial sponsor of the Olympic Games is the Coca Cola corporation. As an article in *Wired* dryly points out, the sponsorship dates so far back that, when it began, Coke still contained cocaine. But isn't it time to reconsider whether manufacturers of sugary beverages should be allowed to associate themselves with physical fitness and sporting achievement? After all, donations from companies that make tobacco products have been excluded since the 1980s (https://www.wired.com/story/public-health-experts-want-the-olympics-to-drop-its-oldest-sponsor/).

Type 2 diabetes and risk of fracture

In a Swedish longitudinal study, older women with type 2 diabetes had a 25% higher risk of bony fracture than women without diabetes. Since women with diabetes had higher bone mineral density and better bone microarchitecture than women without diabetes, skeletal characteristics can't explain the increased risk. However, women with diabetes scored lower on grip strength and gait speed, so perhaps the higher fracture risk is a result of impaired physical function (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2024.25106).

Handwriting in Parkinson's disease

Patients' accounts of their illnesses are especially worth reading if the patient is a professional writer. The poet Anne Carson gives a moving description of her struggles with Parkinson's disease. She found the deterioration in her handwriting particularly upsetting. "I used to take pleasure in writing in notebooks, shelves of them, day after day, year after year. Now the upright strokes bend or break or go in all directions, vowels shrink to blobs, slant loses its smooth smart angle, it all looks embarrassing. I scrub out whole paragraphs in shame" (https://www.lrb.co.uk/the-paper/v46/n16/anne-carson/gloves-on).

Glucose tolerance in adults after prenatal exposure to famine

Four million people died in Ukraine between 1932 and 1933 as a result of a famine deliberately inflicted by Stalin and the Soviet regime. An ecological study links fetal exposure to this famine to an increased risk of type 2 diabetes later in life. Among 10 million Ukrainians born from 1930 to 1938, those who were born in the first half of 1934, and who had therefore been exposed in early gestation to the worst period of the famine, were more than twice as likely to develop type 2 diabetes as those born earlier or later (*Science* doi:10.1126/science.adn4614).

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