education

FROM THE JOURNALS Edited highlights of weekly research reviews

Biliary no mates

Sodium-glucose co-transporter-2 (SGLT2) inhibitors seem to be the talk of the town for type 2 diabetes at the moment, as they may help with weight loss and reduction in cardiovascular risk. Spare a thought for the glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide, semaglutide, etc), which were probably feeling left out even before this latest paper confirming an increase in the risk of gallbladder and biliary diseases with the use of GLP-1 agonists, with an overall relative risk of 1.37.

These are the findings of a systematic review and meta-analysis, which found 76 relevant randomised controlled trials and rated the overall quality of evidence as high. But not all people taking GLP-1 agonists seem to be at risk. Trials of liraglutide and dulaglutide found an increased risk, but not those of oral semaglutide. Using GLP-1 agonists at higher doses (as recommended for weight loss) and for longer duration of treatment (over 26 weeks) also increased the risks of gallbladder and biliary diseases.

JAMA Intern Med doi:10.1001/jamainternmed.2022.0338

Any old iron?

In 2013, the MHRA released a warning about intravenous iron products and the risk of fatal anaphylactic reactions. Infusions should be given only where trained staff and facilities for managing anaphylaxis are available, and patients should be monitored for 30 minutes after each infusion.

A retrospective cohort study aimed to assess the comparative risks of anaphylaxis between intravenous iron products. Iron dextran had the highest rates of anaphylaxis, at 9.8 cases per 10 000 doses. Ferric carboxymaltose had the lowest, at 0.8 cases per 10 000 doses. However, ferric carboxymaltose has a separate MHRA warning about risk of hypophosphataemia leading to osteomalacia and fractures, advising monitoring phosphate levels in those needing multiple high dose administrations, on long term treatment, or with pre-existing risk factors for hypophosphataemia.

Ann Intern Med doi:10.7326/M21-4009

Baricitinib for alopecia

Alopecia areata has been in the spotlight recently after what happened at the Oscars. Two trials of baricitinib, a once-daily oral Janus kinase inhibitor, have just reported outcomes at 36 weeks. The BRAVE AA1 and BRAVE AA2 studies recruited 1200 patients in total. They each had a SALT score—a measure of percentage hair loss (range 0 to 100)—of over 50 and an episode of alopecia areata without recent improvement lasting over six months. Around 35% of those taking baricitinib 4 mg reached the predefined primary endpoint of a SALT score under 20, compared with about 5% of those taking placebo. Acne and raised LDL and HDL cholesterol levels are common adverse events—the studies remain blinded and will continue for up to four years.

ALEXANDRU PAPP / ALAMY

N Engl J Med doi:10.1056/NEJMoa2110343

Incision decisions

This randomised control trial finds that single-incision mini-slings are non-inferior to standard mid-urethral slings for female stress urinary incontinence in terms of patient reported success at 15 months. The mini-slings are associated with less postoperative pain and shorter recovery time than the more widely used mid-urethral slings

An important difference in terms of adverse effects in this study was dyspareunia, reported by 11.7% of those who responded to a questionnaire in the mini-sling group and 4.8% in the mid-urethral sling group. More studies with longer follow-up are needed to answer the questions around long term safety that were raised by the Cumberlege report.

N Engl J Med doi:10.1056/NEJMoa2111815

Bills, bills, bills

If I had to spend hours each day billing insurance companies (or the NHS), I think it would be the last straw. A cross-sectional survey of office based physicians in the US where billing is the norm, asked: "On average, how many hours per day do you spend outside of normal office hours documenting clinical care in your medical record system?" The 1524 respondents said they spent a mean of 1.77 hours per day on this. The research authors' letter discuss that billing-related tasks have a big part to play, and are likely a major factor for why previous research suggests US physicians spend four times longer than in other countries documenting outpatient notes.

JAMA Intern Med doi:10.1001/jamainternmed.2022.0372

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

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STATE OF THE ART REVIEW

Recent advances in the diagnosis and management of cluster headache

CPD READING
0.5 HOURS

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This is a summary of the State of the Art Review: Recent advances in the diagnosis and management of cluster headache, published on bmj.com.

Full article is available at //www.bmj.com/content/376/bmj-2020-059577

Cluster headache is a primary headache disorder consisting of short, frequent, unilateral attacks of facial pain with associated ipsilateral autonomic features and restlessness. The attacks are suspected to be one of the most painful human experiences.

The lifetime prevalence of cluster headache is 0.12% (95% confidence interval 0.10% to 0.15%), although data on one year incidence are limited.[3] Onset can occur at any age but is typically between 20 and 40. Men are more likely than women to have cluster headache, although the exact sex ratio is unclear.

Cluster headache is associated with an increased risk of sleep apnoea, anxiety, depression, and suicidal ideation (around 60%), and a potentially decreased risk of diabetes. It is more common in people who smoke.

Clinical manifestations

The hallmark of cluster headache is the cluster attack, a severely painful unilateral (and typically exclusively one sided or side locked) headache focused behind or around the eye accompanied by ipsilateral autonomic symptoms and restlessness. Cluster attack pain has a stabbing, searing quality, sometimes described as a knife in the eye or a meat grinder behind the eye. Duration, frequency, and particularly restlessness during attacks distinguish it from more common headache disorders (migraine or tension type headache). Table 1 outlines the diagnostic features of cluster headache.

About 80% of patients with cluster headache have the episodic subtype, wherein attacks occur only during a period of weeks to months, often occurring on an annual cycle. The remainder have the chronic subtype, wherein attacks occur regularly throughout the year without remission longer than three months.

Characteristics and other clinical features

Cluster headache is often misdiagnosed, resulting in diagnostic delays. In addition to careful review of the diagnostic criteria, other features of the disease assist in making the correct diagnosis.

Intensity of pain

The pain intensity in cluster headache is renowned. A retrospective online survey of 1604 patients with cluster headache reported the average pain intensity as 9.7 on the 0-10 numerical rating scale, whereas the next highest pain was childbirth at 7.2. In a prospective study the pain intensity of cluster headache was rated an average of 7 out of 10. These differences could suggest that some patients have less severe attacks but may also be explained by differences in study methodology.

Premonitory and inter-ictal symptoms

Pain and associated symptoms are most severe ictally, but patients also report premonitory and inter-ictal symptoms. Most patients describe sensations before an attack, such as ipsilateral aching, lacrimation, or nasal congestion (minutes before), as well as generalised symptoms, such as difficulty concentrating and mood changes (one hour before). Among patients with cluster headache, the localised sensations are commonly referred to as "shadows."

Table 1 | Criteria for cluster headache*

	Parameter	Most common
Attack characteristic		
Pain intensity	Severe or very severe	Very severe (9.7/10)[22]
Laterality	Unilateral and typically side locked	Unilateral and side locked (right > left)[4 23 24]
Location	Orbital, supraorbital, and/or temporal	Orbital[4 22 23]
Associated features (either or both of 1 and 2)	1. At least one ipsilateral to pain: a) conjunctival injection and/or lacrimation; b) nasal congestion and/or rhinorrhea; c) eyelid edema; d) forehead and facial sweating; e) miosis and/or ptosis	Lacrimation, rhinorrhea, nasal congestion, ptosis[4 10 22 23]
	2. Restlessness or agitation	Restless, agitated
Duration (when untreated)	15 to 180 minutes	100 minutes†[4 5 10 24 25]
Frequency	1 every other day to 8 daily	2 to 4 daily[4 10 23]
Number of attacks	A total of five attacks is required before the diagnosis can be made	
Other diagnoses ruled out	Not better accounted for by another headache or facial pain diagnosis	
Subtype		
Episodic	Periods of attacks lasting from 7 days to 1 year with pain-free remission ≥3 months	Prevalence: 80%
Chronic	Attacks for >1 year with pain-free remission <3 months	Prevalence: 20%

*Criteria based on International Classification of Headache Disorders, 3rd edition (ICHD-3).
†Subject to overestimation in retrospective reports[26]

Migraine-like symptoms

Up to two thirds of patients with cluster headache report sensitivity to light and sound, and about a quarter report nausea or vomiting during attacks. Some patients report auras that are quite similar to those described in migraine. Cluster headache can thus be confused with migraine, especially as some patients with migraine show cranial autonomic features. Cluster headache and migraine can best be differentiated by duration (shorter than three hours in cluster headache; longer than four hours in migraine) and restlessness (typically present in cluster headache as discussed below; typically absent in migraine as movement often worsens the headache).

Restlessness and self-injury

Attack related restlessness is one of the most distinctive features of cluster headache. During attacks, patients may pace, rock, vocalize, and carry out other various activities, such as push-ups and running. At times, patients may carry out self-injurious behaviours such as. hitting or rubbing their head, punching the wall, and cutting or piercing the skin. Video 1 on bmj.com shows a striking demonstration of attack related restlessness, as well as reflection on the attack.

Dysautonomia

Systemic and central changes in autonomic tone have been observed in patients with cluster headache, including bradycardia, altered tilt table testing, and nocturnal lipolysis.

Circadian and circannual patterns

About 80% of patients can predict the time of day when attacks occur, the most common being between 2 am and 3 am. Attacks may arise during daytime naps but are more than twice as common during nocturnal sleep, suggesting additional factors besides sleep alone.

Annual rhythmicity is reported in approximately two thirds of patients with episodic cluster headaches and one third of those with chronic cluster headaches.

Attack triggers

The most common trigger for cluster attacks is alcohol, present in 40-80% of patients. Many other triggers, falling into several categories, have been reported (table 2).

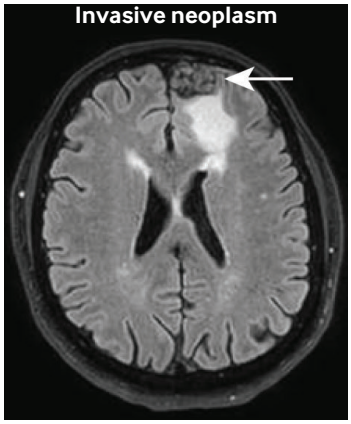
Table 2 | Triggers of cluster attacks

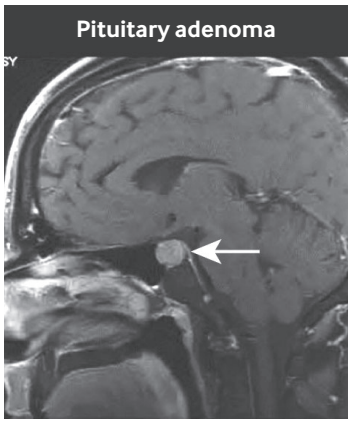
Category	Attack trigger
Chemical[4 10 23 34 47-49]	Alcohol (usually within 1 hour); nitroglycerin, PDE5 inhibitors (eg, sildenafil); strong smells (eg, perfumes, cleaners)
Environmental[4 10 50]	High altitude (eg, flying, mountain climbing); weather changes (eg, temperature, barometer); bright sun (particularly reflecting off snow)
Physiological[10 48]	Sleep (nocturnal sleep › daytime naps); circadian disruption (eg, shift work, jetlag, daylight savings); stress or relaxation (drop in hormones after stress); menstruation, menopause, post partum; low testosterone concentrations

PDE5=phosphodiesterase type 5

Differential diagnosis

Two considerations are important in the differential diagnosis of cluster headache: primary headache disorders with similar features and secondary headaches that present with cluster-like headaches.





Primary headache disorders

Cluster headache is part of a group of five disorders called trigeminal autonomic cephalalgias; these all present quite similarly but differ in duration, frequency, and treatment. The other four trigeminal autonomic cephalalgias are hemicrania continua, paroxysmal hemicrania, short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, and short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms. Like cluster headache, the other trigeminal autonomic cephalalgias present with ipsilateral autonomic features and, at least for hemicrania continua and paroxysmal hemicrania, restlessness.

Secondary causes

These include pituitary adenomas, meningiomas, arteriovenous malformations, and other lesions (figure). These lesions can present with attacks that are indistinguishable from primary cluster headache, but treatment of the lesions can be curative.

Investigation

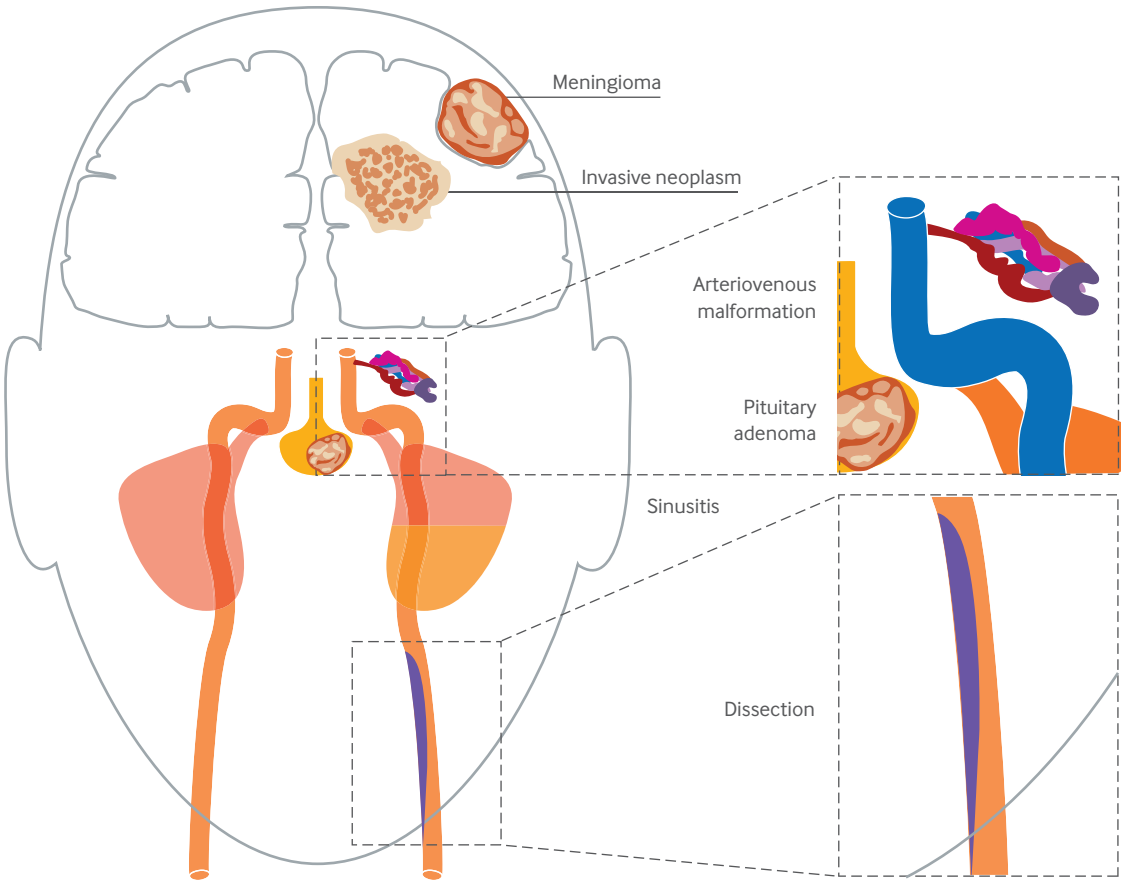
The recommended investigations for cluster headache consider the differential diagnoses. A consensus statement from the European Headache Federation recommends magnetic resonance imaging of the brain in all patients with cluster headache (with detailed views of the cavernous sinus and pituitary area); in refractory patients, it recommends consideration of magnetic resonance angiography of the head and neck, pituitary laboratory testing, a sleep study for obstructive sleep apnoea, and, in patients with Horner syndrome, imaging of the lung apex.

Treatment

Treatments for cluster headache can be divided into acute or "as needed" therapies, bridge or "short term preventive" therapies that can be taken only for short courses, and preventive therapies. Below, we discuss acute, bridge, and preventive therapies listed by the American Headache Society (published in 2016) and European Federation of Neurological Societies (published in 2006), as well as clinical trial data published since 2016.

Acute treatment

The first line acute treatments for cluster headache are subcutaneous sumatriptan and oxygen. Expert guidelines have given both of these



Secondary causes of cluster-like headaches. Cluster headache is a primary headache disorder with no known underlying lesions. However, in rare cases, secondary or "symptomatic" causes exist that are indistinguishable from primary cluster headache, and treatment of the lesion results in resolution of the headaches. On the left are two cases of secondary cluster-like headaches from the authors' personal experiences: an invasive metastatic neuroendocrine tumour (the headaches resolved after resection of the left frontal tumour) and a pituitary tumour or more specifically a prolactinoma (the headaches completely remitted once cabergoline was started to correct the prolactinaemia). On the right is a diagram of the more frequent causes of secondary cluster-like headaches from reviews of case reports.[55-57] The imaging for the pituitary tumour is reprinted with permission[58]

treatments level A evidence, and surveys of patients have generally found triptans and oxygen to be the most effective acute treatments (table 4, bmj.com).

Subcutaneous sumatriptan

Subcutaneous sumatriptan may be the single most effective acute treatment according to data from surveys of patients. More rapid forms of administration of the triptans are preferred, starting with subcutaneous sumatriptan, followed by nasal zolmitriptan and nasal sumatriptan, followed by oral zolmitriptan. The triptans cause vasoconstriction via activation of the 5HT1B receptor and are not recommended in patients with vascular disorders such as myocardial infarctions, strokes, and uncontrolled hypertension.

Oxygen

Inhaled oxygen effectively treats attacks at flow rates of 6 L/min and 12 L/min. Higher flow rates are generally preferred, with a survey of patients suggesting that flow rates above 10 L/min were more efficacious than those under 10 L/min and as efficacious as injectable sumatriptan. Oxygen has a high effectiveness and low side effects compared with other acute drug treatments. Contraindications are rare but include the risk of fire: smoking and open flames are prohibited when using oxygen.

Non-invasive vagus nerve stimulation

Non-invasive vagus nerve stimulation was recently shown in two clinical trials to be effective in aborting attacks in patients with episodic but not chronic cluster headache. Like oxygen, non-invasive vagus nerve stimulation can be safely used on a regular basis. Contraindications include implanted medical devices (for example, pacemaker or hearing aid implants) and implanted metal near the neck (for example, carotid stent or cervical bone screw).

Transitional treatments

Transitional or bridge therapies can provide relatively quick relief for a brief period. They may also be used to terminate periods in episodic cluster headache or induce a period of remission in chronic cluster headache (table 5, bmj.com).

Corticosteroids

Corticosteroids have been delivered via occipital nerve blocks and oral tablets; both methods of delivery have shown benefit using a variety of corticosteroid types and dosages. Occipital and suboccipital nerve blocks were investigated in a meta-analysis, showing a relative risk ratio of 4.86 for freedom from pain at one month compared with control, as well as an overall 50% freedom from pain at one month. The exact components of the blocks differed widely. A recent randomised controlled trial showed significant improvement with a 17 day course of oral prednisone (starting at 100 mg daily for five days, then titrating down by 20 mg every three days).

Dihydroergotamine

Dihydroergotamine is an ergot compound with clinical effects in cluster headache, likely owing to its serotonergic activity. Several retrospective analyses support its use in cluster headache but it is not specifically recommended by current guidelines.

Preventive treatment

Generally, patients with chronic symptoms need continual preventive therapy, whereas patients with episodic symptoms need it only during their cluster period. Preventive treatment usually does not eliminate attacks but reduces their frequency, intensity, or both, necessitating continued access to effective abortive therapy. Table 6 (bmj.com) shows the treatments for which good evidence in cluster prevention exists.

Verapamil

Verapamil is a calcium antagonist and considered the first line preventive. In controlled trials, verapamil 120 mg immediate release three times daily reduced headache burden by at least 50% after one to two weeks of treatment in both episodic and chronic cluster headache. Verapamil can prolong the cardiac PR interval so electrocardiographic monitoring is recommended before initiation, one to two weeks after an increase in dose, and every six months thereafter.

Lithium carbonate

Lithium carbonate is primarily used for the management of mood disorders. Lithium interrupts G-protein signalling, implicating several neurotransmitter systems, and affects hypothalamic and sleep function. Lithium is less commonly used than other modern preventives, given its narrow therapeutic range and undesirable side effect profile, including somnolence, thyroid dysfunction, and diabetes insipidus.

Melatonin

Melatonin is a circadian hormone produced by the pineal gland best known for its role in sleep. Nightly melatonin (10 mg orally) was reported to terminate cluster attacks in half of participants in a placebo controlled trial.

Civamide

Civamide (zucapsaicin) is a synthetically produced cis isomer of capsaicin, the naturally occurring "active ingredient" of hot peppers. Civamide inhibits pain transmission by activating the vanilloid 1 receptor (or transient receptor potential cation channel subfamily V member 1 receptor) and by blocking calcium channels. Nasal burning and lacrimation are commonly reported adverse events.

Topiramate

Topiramate is used widely in neurology to treat epilepsy, neuropathy, tremor, and migraine. It has several pharmacological targets, including sodium and calcium channels and the γ-aminobutyric acid (GABA)-A receptor. Open label trials of topiramate in cluster headache support clinical efficacy, although no controlled studies exist. In the most recent prospective study investigating topiramate in cluster headache, the average dose of 273 (range 100-400) mg induced remission in nine of 12 patients with episodic cluster headache in an average of 10.7 (6-18) days, representing a 51% reduction in the duration of remaining cluster period.

Baclofen

Baclofen is a GABA-B receptor agonist. It is best known as a muscle relaxer, but clinical effects in pain conditions such as trigeminal neuralgia, glossopharyngeal neuralgia, and post-herpetic neuralgia support its consideration in headache disorders. In an open label study of baclofen in episodic cluster headache, 12 of 16 participants were attack-free after one week of treatment at a dose of 15-30 mg divided three times daily.

Galcanezumab

Galcanezumab, a humanized monoclonal antibody against CGRP, is the newest preventive drug available for episodic cluster headache. In weeks 1 to 3 after injection, 71% of patients with episodic cluster headache who received galcanezumab had a 50% or greater reduction in weekly attacks, compared with 53% who received placebo. Importantly, the dose for cluster headache is 300 mg monthly, whereas the dose for migraine is only 120 mg. Galcanezumab was not as effective in a separate trial for chronic cluster headache. However, given the refractory nature of chronic cluster headache in many patients, some authors advocate its use in chronic cluster headache given its effectiveness in isolated cases.

Neuromodulation

The non-invasive vagus nerve stimulation device was shown to reduce attack frequency significantly in cluster headache when used as adjunctive therapy compared with standard of care alone. Invasive neuromodulation devices (occipital nerve stimulation, sphenopalatine ganglion stimulation, and deep brain stimulation) are discussed in the "Refractory" section (bmj.com).

Patient directed disease management

Patients with cluster headache may consume coffee or energy drinks as an acute treatment; both of these contain caffeine, and energy drinks contain other compounds such vitamin B12 and taurine. Various vitamin regimens are taken by patients for disease prevention, high dose vitamin D (starting at 50 000 IU daily with a maintenance dose of 10 000 IU daily) being one of the more common ones. Vitamin D concentrations have been reported to be low in people with cluster headache, although the role for supra-supplementary dosing in treatment needs further investigation. According to the Institute of Medicine, patients should avoid doses of vitamin D over 125-150 nmol (slightly above the normal range of 30-100 nmol), in part because of the risk of hypercalcaemia.

For more than two decades, patients with cluster headache have been using classic serotonergic psychedelics, such as lysergic acid diethylamide (LSD) and psilocybin (found in so called "magic mushrooms"), in disease management. Unlike conventional medications, this drug class is reported to induce long term (months or years) reduction of headache burden after limited administration (for example, three doses). Importantly, sub-hallucinogenic doses and non-hallucinogenic types of these psychedelic drugs are also reported to have long lasting therapeutic effects. The first clinical trials in cluster headache have begun with LSD and psilocybin. These studies all exclude patients with serious medical disease or psychotic or manic disorders, as psychedelics could lead to serious adverse events in these groups.

Competing interests: See bmj.com.

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HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

A video of a patient with a cluster headache attack was made specifically for this article (https://www.bmj.com/content/376/bmj-2020-059577)

RATIONAL TESTING

Investigating hypertension in younger patients

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. To suggest a topic for this series, please email us at practice@bmj.com.

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WHAT YOU NEED TO KNOW

- Secondary hypertension may account for up to 30% of diagnoses of young onset hypertension
- Thyroid dysfunction, renal parenchymal disease, and renal artery stenosis secondary to fibromuscular dysplasia are the most common causes of secondary hypertension in younger patients
- Testing for 24 hour urinary metanephrines should be carried out only if the patient has phaeochromocytoma symptoms, clinical signs, or relevant family history
- Random (spot) serum cortisol tests are usually uninformative. Consider late evening salivary cortisol if available
- If treating patients with young onset hypertension empirically, revisit a diagnosis of secondary hypertension following post-treatment blood tests, or if blood pressure control is not achieved or deteriorates

A 38 year old patient attends her GP reporting several high blood pressure readings at home. The GP records a clinic blood pressure of 159/101 mmHg.

Hypertension is often thought of as a disease of older age, but it occurs across all adult ages, including in younger patients. In the US, 22.4% of people aged 18-39 are estimated to have a blood pressure of above 130/80 mmHg.[1] The 2018 Health Survey for Health for England found that 2.6% of people aged 16-24 and 12.2% of those aged 35-44 had hypertension (on antihypertensive medication and/or blood pressure above 140/90 mmHg).[2] Various guidelines define young onset differently. This article uses the definition in guidelines from the UK's National Institute for Health and Care Excellence (NICE), which is hypertension in patients under the age of 40.[3]

Essential hypertension remains the most common cause of hypertension, even in young onset hypertension, but secondary hypertension—which has an underlying pathological cause—accounts for 5% to 30% of cases of young onset hypertension.[4-6] Secondary hypertension is not a diagnosis in itself, but rather a collective term for hypertension caused by a defect in one or more of the physiological systems involved in blood pressure homeostasis. Causes of secondary hypertension can be divided broadly into seven categories (table 1, bmj.com).[4 6] In young onset patients, the most common causes are thyroid dysfunction, renal parenchymal disease, renal artery stenosis secondary to fibromuscular dysplasia, and (starting at around age 40) primary aldosteronism (primary hyperaldosteronism).[5] In the general adult population, the most prevalent causes of secondary hypertension are obstructive sleep apnoea (>5-15% prevalence in hypertensive patients), renal parenchymal disease (1.6-8.0%), primary aldosteronism (1.4-10%), renal artery stenosis (1.0-8.0%), and thyroid disease (1-2%).[4]

The underlying conditions associated with secondary hypertension have health consequences if left untreated, therefore young onset hypertension warrants further investigation. Patients with young onset hypertension face more years at risk of cardiovascular disease than patients in whom hypertension emerges later in life. In a recent study of nearly 20 000 case-control normotensive/hypertensive patient pairs, the all-cause mortality hazard ratio for patients whose hypertension started before the age of 45 was twice that of patients diagnosed with hypertension at 65 or more years of age (2.6 versus 1.3).[7] Furthermore, some causes of secondary hypertension carry additional risks beyond the physiological impact of chronically raised blood pressure.[8 9] Specific (possibly curative) treatment may be available, early treatment may prevent irreversible processes such as vascular remodelling, and, if surgical interventions are an option, younger patients are likely to have better outcomes.[4 8] However, a significant delay often occurs before secondary hypertension is diagnosed: typically two to four years, but sometimes decades.[4-14]

Confirm diagnosis

The first step in any patient with suspected undiagnosed hypertension (eg, an elevated office blood pressure reading) is to clinically confirm the diagnosis. Arrange serial blood pressure measurements, either with an automated device over a period of 24 hours (ambulatory blood pressure monitoring, ABPM), or with home blood pressure monitoring (HBPM), where the patient records their blood pressure with a validated device[15] twice daily for at least four, and ideally seven days. ABPM may be preferable to HBPM in young onset patients because it can identify patients who show no nocturnal drop in blood pressures.[3 16] These individuals are more likely to have secondary hypertension than individuals with a nocturnal dip and are at increased risk of chronic kidney disease and cardiovascular disease.[3 16]

Severe hypertension

Severe hypertension (typically defined as a clinic blood pressure greater than 180/120 mmHg confirmed from two to three readings within a consultation) in young onset patients is secondary hypertension unless proved otherwise.[17 18] Severe hypertension with signs of accelerated (malignant) hypertension (retinal haemorrhage or papilloedema) or red flags such as new onset confusion, chest pain, clinical signs of heart failure, or acute kidney injury warrants referral within the day, as does hypertension with suspected phaeochromocytoma (eg, postural hypotension, palpitations, excess sweating).[3] If the patient does not need on-the-day referral, start investigations for end organ damage (see below) and initiate treatment if damage is identified, even if confirmation of hypertension is pending. In newly confirmed severe but non-malignant young onset hypertension, referral to secondary care is advisable, as is ongoing close monitoring of blood pressure in primary care.

Further assessment of secondary hypertension in primary care

Once hypertension is confirmed, further examinations and tests aim to check for end organ damage and identify patients with secondary hypertension. Table 1 (bmj.com) lists examination findings in secondary hypertension and table 2 summarises suggested initial investigations in primary care.[3-18]

Although rare, coarctation of the aorta can cause young onset hypertension. Assess for detectable radio femoral pulse delay, absent or faint femoral pulses, or, more rarely, radio radial pulse delay or a significant (>15 mmHg) discrepancy in blood pressure between both arms. These indicate coarctation of the aorta until proved otherwise. Refer urgently for specialist cardiology assessment which would typically include cardiac magnetic resonance imaging and/or a transoesophageal echocardiogram.[8]

Auscultate for renal bruits 2-3 cm above and bilaterally to the umbilicus,[19] which suggest renal artery stenosis; the prevalence of abdominal bruits in patients with angiographically proved renal stenosis varies between 78% and 87%.[20] Request ultrasonography of the kidney, bladder, and ureters (US-KUB) although this can only detect the consequences of stenosis (eg, renal atrophy from under-perfusion) and a normal US-KUB does not exclude renal artery stenosis. Definitive diagnosis requires secondary care investigations such as renal artery duplex ultrasound or gadolinium induced magnetic resonance angiography. Arrange a US-KUB to assess for renal parenchymal disease if clinical examination reveals a ballotable kidney or kidneys.

Consider hypertension induced by medication, illicit drugs, herbal remedies, and certain foods and supplements

Consider hypertension induced by prescribed and over-the-counter medication, illicit drugs, herbal remedies, and certain foods and supplements.[5 6] Common causes include non-steroidal anti-inflammatory drugs, anti-depressants (eg, venlafaxine or monoamine oxidase inhibitors), glucocorticoids, sex hormones (in particular oral combined hormonal contraception), alcohol, caffeine, cocaine, and glycyrrhizic acid (the main active ingredient in liquorice).[21]

Table 2 | Recommended initial primary care investigations in young onset hypertension*

Recommended tests	
Albumin:creatinine ratio	Proteinuria may indicate hypertension mediated organ damage (HMOD)
Urine dipstick testing	Proteinuria and/or haematuria may indicate renal parenchymal disease (in absence of a urinary tract infection)
Electrolytes and creatinine, eGFR	Abnormal electrolyte profile may suggest secondary hypertension (eg, hypokalaemia and primary aldosteronism). Reduced eGFR indicates HMOD
HbA_{1c}/fasting blood glucose **Total cholesterol and HDL cholesterol**	Diabetes and hypercholesterolaemia increase risk of cardiovascular disease (and are used in cardiovascular risk scoring). Diabetes modifies hypertension management. Non-diabetic hyperglycaemia and hypercholesterolaemia are suggestive of metabolic syndrome
Thyroid function tests	Thyroid dysfunction is a common cause of secondary hypertension. Both hypothyroidism and hyperthyroidism can result in raised blood pressure
Haemoglobin and/or haematocrit/full blood count	Abnormalities in blood viscosity have been implicated in hypertension and cardiovascular disease. Anaemia is a common complication of chronic kidney disease. Polycythaemia vera is a rare cause of secondary hypertension
12-lead ECG	LVH indicates HMOD
Recommended examinations	
Fundal examination	Hypertensive retinopathy indicates HMOD
Body mass index (BMI)	High BMI is associated with obstructive sleep apnoea, a cause of secondary hypertension. Obesity is associated with hypertension (metabolic syndrome)
Assessment for radio-radial and radio-femoral delay or absent femoral pulses	Presence of delays or absence of femoral pulse indicate coarctation of the aorta (CoA) unless proved otherwise
Assessment for murmurs/bruits (cardiac, intrascapular, and abdominal)	Aortic regurgitation and intrascapular murmurs are associated with CoA Renal bruits indicate likely renal artery stenosis
Left and right brachial blood pressures	Difference ≥20 mmHg may indicate CoA (proximal to left subclavian artery, rare) or peripheral arterial disease (very rare in younger patients). Further blood pressure measurements should be made from the arm with higher blood pressure readings

*Derived from UK, US, and European guidelines on management of hypertension.[3-18] Tests in bold are recommended as part of the initial workup by NICE,[3] to be performed concurrently with ABPM/HBPM. CKD=chronic kidney disease; CVD=cardiovascular disease; HMOD=hypertension-mediated organ damage; LVH=left ventricular hypertrophy; UTI=urinary tract infection

Biochemical abnormalities in secondary hypertension

Biochemical abnormalities are associated with some causes of secondary hypertension. These can be seen on initial screening and in response to starting treatment. Therefore, re-check renal function including serum potassium, sodium, and creatinine approximately two weeks after starting treatment (or treatment dose up-titration).

Thyroid dysfunction is one of the most common causes of secondary hypertension in young onset patients.[5] UK and European guidelines do not suggest including thyroid function tests as part of baseline investigations,[3 18] however, guidelines from the US recommend ruling out hypothyroidism and hyperthyroidism as causes of secondary hypertension.[17] US and European guidelines advise obtaining a full blood count (or haemoglobin levels and/or a haematocrit).[17 18]

Hypokalaemia

The textbook biochemical picture of primary aldosteronism includes hypokalaemia (typically mild) with a serum sodium level at the high end of the normal range or slightly elevated. However, large scale prospective studies have shown that spontaneous hypokalaemia (≤3.7 mmol/L) is present in only 41% to 57% of patients.[22 23] Refer to secondary care for further testing (table 1, bmj.com) patients with spontaneous hypokalaemia or new or worsening hypokalaemia induced by even a small dose of a diuretic.

Similarly, in high concentrations, cortisol can exhibit mineralocorticoid (aldosterone-like) activity, so hypokalaemia and/or stigmata of Cushing's syndrome in young onset hypertension should prompt investigation of possible hypercortisolaemia.

Renal function deterioration

A reduction in renal function (as shown by a fall in estimated glomerular filtration rate, eGFR, or rise in serum creatinine levels) following initiation of an ACE inhibitor or angiotensin II receptor blocker (ARB) is common, typically mild, and not of clinical concern. However, an excessive drop in eGFR (>25%), or serum creatinine increase greater than 30%, is suggestive of renal artery stenosis (typically bilateral).[24 25] Fibromuscular dysplasia accounts for 10-30% of renal artery stenosis, and in young onset hypertension fibromuscular dysplasia is significantly more likely to be the cause of renal artery stenosis than atherosclerotic renal artery stenosis.[26] The typical patient with renal fibromuscular dysplasia is female (80-90% of cases) and under the age of 50.

Biochemical abnormalities mentioned in this section and others found in secondary hypertension, as well as advisable next step investigations, are summarised in table 1, bmj.com.

Unnecessary tests

Beyond the investigations suggested in table 2, few further investigations are indicated in primary care, and some are unnecessary (see below).

Twenty four hour urine collection in phaeochromocytoma

A 24 hour measurement of urinary fractionated metanephrines (24-h UMN) has high sensitivity (86-97%) and good specificity (69-95%) for phaeochromocytomas.[27] However, 24-h UMNs should not be part of the routine investigation of young onset hypertension, and should only be done in the presence of clinical signs and symptoms of phaeochromocytoma or suggestive family history (box 1).[4-6] Measurement of plasma free metanephrines has a higher specificity than 24-h UMN but collection should be made from patient fully recumbent for at least 30 minutes before sampling.[27]

Box 1 | Phaeochromocytoma (PCC)

- A PCC is a catecholamine secreting tumour arising from adrenomedullary chromaffin cells; tumours can also arise from extra-adrenal chromaffin cells (paraganglioma)
- PCCs and paraganglioma are rare (but life threatening) causes of secondary hypertension, accounting for 0.2-0.6% of cases
- The secreted catecholamines are principally adrenaline and noradrenaline, accounting for the typical "sympathetic" signs and symptoms of PCCs
- Signs and symptoms include the so called "5 Ps" of PCCs[4]:
  - paroxysmal hypertension
  - palpitations
  - perspiration
  - pallor
  - pounding headache
- Other signs and symptoms include facial flushing, orthostatic hypotension, and syncope/pre-syncope. These are often paroxysmal and can be precipitated by any form of stress (eg, exercise, emotion, surgery)
- Family history of PCC, personal or family history of genetic syndromes associated with PCC (MEN2; von Hippel Lindau, neurofibromatosis), and suspicious adrenal lesions (often adrenal incidentalomas) all suggest PCC in the context of young onset hypertension[4 6]

Random (spot) cortisol measurement

Although serum cortisol levels can be ordered in primary care, random (spot) cortisol tests are of limited clinical value and assessment for cortisol excess should be performed on a late evening sample, often referred to as a "midnight cortisol."[28] Serum cortisol testing is therefore unsuitable in primary care, even if Cushing's syndrome is suspected. Twenty four hour urinary cortisol testing is sometimes available, but is demanding on patient time and diligence, time consuming to organise, and has a lower sensitivity and specificity for hypercortisolaemia than other methods.[28] If available, salivary cortisol is a more practical alternative, as it is a non-invasive test, better suited to testing during antisocial hours (as the sample can be stored at 4°C for up to two weeks), and has better specificity than 24 hour urinary cortisol.[28]

Evaluation of aldosterone and renin activity

The key investigation in biochemical confirmation of primary aldosteronism is the aldosterone-to-renin ratio (ARR), also known as the plasma aldosterone concentration to plasma renin activity (PAC/PRA) or the aldosterone/PRA ratio (APR). Aldosterone and renin (levels and/or ratio) tests require careful pre-test medication verification and possible alteration, strict collection criteria, and rapid laboratory processing (within one hour of collection), all of which make them unsuitable for reliable completion in primary care.

Who to refer?

The three major guidelines on hypertension advise clinicians to consider specialist referral for adults with young onset hypertension and/or in whom secondary hypertension is presumed or needs excluding.[3-29] Supplementary table 1 (bmj.com) summarises other situations in which early secondary care involvement is advisable and where secondary hypertension may be suspected but initial management in primary care may be appropriate.

In general, if the initial assessment finds no evidence of secondary hypertension and no immediate clinical concerns, initial empirical management can be started in primary care with appropriate follow-up. In these patients a "second diagnostic look"[4] is needed, as clues to secondary hypertension may emerge after treatment has started. After initiating antihypertensive therapy, consider secondary hypertension as per the scenarios in box 2.[4]

Box 2 | When to take a "second diagnostic look"[4]

- An excessive drop in potassium with a small dose of a diuretic (primary aldosteronism or other endogenous or exogenous mineralocorticoid excess)
- Excessive decrease in GFR with a small dose of an ACE inhibitor or angiotensin II receptor blocker
- Remarkably resistant hypertension
- Blood pressure that decreases with treatment but remains excessively labile.

Consider repeating the examinations and investigation suggested in table 1 while exploring the patient's adherence to medication and lifestyle changes. Consider again a diagnosis of secondary hypertension if blood pressure control suddenly deteriorates in a patient whose readings were previously stable while taking antihypertensives.

Sleep apnoea/sleep hypoventilation

Although age is a risk factor for sleep apnoea, hypopnoea, or hypoventilation syndromes, young patients are susceptible. Obstructive sleep apnoea/hypopnoea syndrome (OSAHS), and the related obesity hypoventilation syndrome (OHS) are thought to be underdiagnosed causes of secondary hypertension in young onset hypertension.[30 31] OSAHS and OHS should be considered in young onset hypertension in patients with a body mass index ≥30 kg/m^2 and/or suggestive symptoms (eg, snoring, witnessed apnoea, excessive sleepiness). Further investigations are discussed in table 1. Treatment includes weight loss, nocturnal continuous positive airway pressure, or non-invasive ventilation (supplementary table 1, bmj.com).

Resistant hypertension

Resistant hypertension has a strong association with secondary hypertension.[4 6] The NICE guidelines define resistant hypertension as hypertension that remains uncontrolled "in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a calcium channel blocker and a thiazide-like diuretic."[3] Patients with resistant hypertension may be started on a fourth agent (eg, low dose spironolactone or an α-blocker such as doxazocin),[3] but for patients with young onset resistant hypertension, we recommend a specialist referral.

Outcome

The patient's hypertension was confirmed by HBPM. Initial serum electrolytes showed hypokalaemia (serum K^+ 3.3 mmol/L) but were otherwise unremarkable and the patient was referred to the local hypertension clinic. The patient's aldosterone level was 423 pmol/L with suppressed renin activity at <0.15 nmol/L/h. Her kidney ultrasound scan was normal but a computed tomography scan of the adrenal glands identified a left sided adrenal adenoma of 13 mm. The patient was referred to the endocrinology department and had a saline suppression test that was consistent with primary aldosteronism. Subsequent adrenal vein sampling lateralised to the left side and confirmed primary aldosteronism caused by the left sided adrenal adenoma. At this point the patient's blood pressure was 125/89 mmHg with a single agent (amlodipine 5 mg once daily). The patient has been scheduled for ultrasound guided ablation of her adenoma.

For patients with young onset resistant hypertension, we recommend a specialist referral

HOW THIS ARTICLE WAS MADE

We searched PubMed for relevant articles using the following search terms: secondary hypertension; renal artery stenosis; renal hypertension; primary (hyper)aldosteronism; metabolic hypertension; metabolic syndrome; ph(a)eochromocytoma; adrenal incidentalomas, Cushing, thyroid hypertension, fibromuscular dysplasia, coarctation, abdominal bruit(s). We also searched BMJ Best Practice and NICE guidelines and Clinical Knowledge Summaries for (secondary) hypertension, phaeochromocytoma, renal artery stenosis and Cushing.

We identified further relevant articles from references therein and from targeted searches in PubMed.

EDUCATION INTO PRACTICE

- When considering a patient with young onset hypertension, do you consider secondary hypertension before diagnosing essential hypertension?
- Audit your practice for 24 hour urinary metanephrine tests; what clinical indications did patients have for the test?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Two patients with young onset hypertension who were seen in GR's hypertension clinic reviewed a draft of this article. Based on their feedback, we revised the manuscript to emphasise the importance of recognising young onset hypertension as a condition meriting specific investigation, and added more detailed advice on when to consider referral for young onset hypertension.

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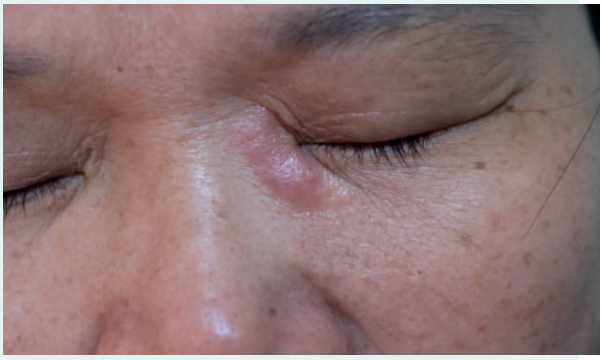
MINERVA

Angiolupoid sarcoidosis on the paranasal area

This is angiolupoid sarcoidosis on the left paranasal area of a woman in her 50s. She presented with a four month history of an erythematous plaque (1.8 cm×0.8 cm) with telangiectasia. She reported no pain or itchiness.

Skin biopsy showed a non-infectious naked granuloma, consistent with sarcoidosis. A gallium scan (radionuclide imaging) showed bilateral sarcoid involvement of parotid and lacrimal glands (panda sign) and bilateral hilar and right paratracheal lymph node involvement (lambda sign). Pulmonary function tests showed decreased lung function with a restrictive pattern, despite no obvious respiratory symptoms on history or examination.

Angiolupoid sarcoidosis is characterised by an erythematous plaque with prominent telangiectasia, particularly on one side of the nasal bridge towards the medial canthus. Its unique skin manifestation and site of predilection might help to differentiate it from other diagnoses, including basal cell carcinoma and mycobacterial and fungal infections. Early diagnosis and treatment of this uncommon variant of cutaneous sarcoidosis, which has a higher risk (86%) of eye, lung, and lymph node involvement, might prevent serious systemic complications.



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Patient consent obtained.

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

If you would like to write a Case Review or Spot Diagnosis for Endgames, please see our author guidelines at http://bit.ly/29HCBAL

Long term use of cannabis

People who smoke cannabis for many years are at greater risk of developing cognitive deficits in midlife, according to a longitudinal study from New Zealand. Among 1000 people born in the 1970s and followed until the age of 45, long term users of cannabis experienced a mean decline of 5.5 IQ points from childhood. This deterioration could not be accounted for by the use of tobacco, alcohol, or other illicit drugs, or by socioeconomic status in childhood (*Am J Psychiatry* doi:10.1176/appi.ajp.2021.21060664).

Ultrasound guided arthrocentesis

Performance on most tasks is improved by having a clear view of what's going on. A small trial shows that this is true of arthrocentesis of elbow, wrist, or ankle joints. Patients with suspected joint effusions were randomly allocated to landmark guided or ultrasound guided procedures. More than 90% of ultrasound guided procedures were successful, compared with 60% in the landmark guided group (*Am Emerg Med* doi:10.1111/acem.14396).

Basal cell carcinoma

Basal cell carcinoma is the most frequently diagnosed malignancy worldwide. Data from the Netherlands show that incidence has doubled over the past 20 years. Rates in young people have stabilised recently, which may be a first sign that the incidence is levelling off. However, it continues to rise in people over 50 (*Br J Dermatol* doi:10.1111/bjd.20871).

Intensive lifestyle intervention in people with type 2 diabetes

More than 5000 people with type 2 diabetes who were overweight or obese were randomised either to an intensive lifestyle intervention aimed at weight loss, or to a programme of diabetes support and education. Over 10 years, no differences were seen in mortality or morbidity. Participants in the lifestyle intervention group who lost 10% or more of their body weight reduced their mortality by a fifth (*Diabetes Care* doi:10.2337/dc21-1805).

Autism and suicide

Analysis of records of coroners' inquests from two regions of England found evidence of autism more often in those who died by suicide than would be expected from the prevalence of autism in the general population. Follow-up interviews with the next of kin confirmed that autistic traits are substantially over-represented in people who take their own lives (*Br J Psychiatry* doi:10.1192/bjp.2022.21).

Autistic traits are substantially over-represented in people who take their own lives

Packaging of medication

A qualitative study of older people living at home explores the difficulties they have with taking their prescribed medication. Many of the problems stem from the way drugs are packaged. Apart from being hard to open, packaging varies between different preparations of the same drug, which often causes confusion and anxiety. The investigators call for a patient centred approach and the involvement of older people in the design of medication packaging (*Age Ageing* doi:10.1093/ageing/afac050).

Anti-rheumatic drugs and Parkinson's disease

Last year, a registry study from Sweden reported that people previously diagnosed with rheumatoid arthritis were less likely to develop Parkinson's disease than those without such a diagnosis (*J Parkinson's Dis* doi:10.3233/JPD-202418). A study from Finland finds that this link can't be explained by exposure to disease modifying anti-rheumatic drugs, including sulfasalazine, methotrexate, gold, immunosuppressants, and corticosteroids. Chloroquine and hydroxychloroquine, however, were exceptions and were associated with a decrease in risk of Parkinson's disease (*Neurology* doi:10.1212/WNL.0000000000013303)

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