education

RESEARCH REVIEWS Fortnightly round up from the leading medical journals

Vitamin D shines in treatment for early multiple sclerosis

There are so many studies published about vitamin D about a dozen each day—it's hard to keep up. One that stands out is a double-blind randomised controlled trial of high dose vitamin D in people with early signs of multiple sclerosis. An acute first episode such as optic neuritis or transverse myelitis with typical findings on imaging is known as

clinically isolated syndrome typical for multiple sclerosis (CIS). In the

trial 316 people with CIS and a vitamin D level below 100 nmol/L were randomised to receive 100 000 IU colecalciferol or placebo every two weeks.

After two years, the rates of disease activity—a clinical relapse or new signs on magnetic resonance imaging (MRI)—were observed in 60.3% of the vitamin D group and 74.1% of the placebo group (hazard



Usable FIT return within 3 months, by planning tool and deadline status

Deadline day

"I don't need time. I need a deadline," the jazz composer Duke Ellington once said. Perhaps inspired by this, the bowel cancer screening programme in Scotland added a sentence to faecal immunochemical test (FIT) invitation letters asking people to return it before a deadline of one, two, or four weeks. This led to faster FIT returns, fewer reminder letters being sent out, and "marginally higher" return rates at three months—from 66% to 68% with a two-week return deadline. Those sent a letter with a planning tool and no deadline were less likely to return their FIT kits (see figure).

Lancet doi:10.1016/S0140-6736(24)02813-7

ratio 0.66 (95% confidence interval 0.50 to 0.87)). • *JAMA* doi:10.1001/ jama.2025.1604

Getting prepped for once yearly PrEP

The PURPOSE 1 and 2 trials have previously found that 6-monthly dosing of lenacapavir-based HIV pre-exposure prophylaxis (PrEP) was highly effective at reducing HIV infection in high risk populations.

A phase 1 study has started assessing the potential for once yearly PrEP: 40 participants in North America, mostly white men with no comorbidities. received intramuscular lenacapavir and had the drug's blood concentrations monitored over the course of a year. Median lenacapavir levels compared favourably with those found in the PURPOSE trials, paving the way for larger, more detailed trials. Lancet doi:10.1016/S0140-6736(25)00405-2



CLINICAL PICTURE

Clearly demarcated erythematous rash

This man in his early 70s presented with a two year history of an itchy rash on his lower limbs. He had initially had a diagnosis of psoriasis and was treated with topical clobetasol propionate.

Although the itch improved with this treatment, the rash persisted and

worsened. On examination, there was clearly demarcated erythema on both feet and lower legs, and thickening, deformation, and discoloration of the toenails (figure). Fungal cultures of the skin identified *Trichophyton rubrum*, and the diagnosis was revised to tinea incognito with onychomycosis. Tinea incognito refers to a superficial dermatophyte infection that has been inappropriately treated with topical steroids, leading to an atypical clinical appearance. This patient was treated with itraconazole (200 mg twice a day for seven days each month) orally for six months, and topical antifungal cream twice a day for one month, with substantial



A comforting nudge in intensive care

"Do you think this patient will be alive six months from now?"

A cluster randomised trial asked intensivists this question (and made them record their justification in patients' notes) to see if this low cost nudge would lead to reduced length of hospital stay for patients in intensive care.

In theory, nudging clinicians to consider and discuss comfortfocused care in addition to intensive care, where appropriate, could lead to shorter hospital stays. This didn't materialise, but there was a small increase

in the number of patients discharged to a hospice in the nudge arm of the study. JAMA Intern Med doi:10.1001/ jamainternmed. 2025.0090



from the first randomised controlled trial of automated insulin delivery (AID) for people with type 2 diabetes.

The trial recruited 319 adults with type 2 diabetes who were receiving multiple daily insulin injections and allocated them to switch to an AID or to continue their current treatment. Those allocated to the AID had an average 0.9% reduction in HbA1c at 13 weeks, compared with a 0.3% reduction in the control group, with those with higher baseline HbA1c tending to see the largest reductions. Most (93%) in the AID group continued using the

system for the 13-week duration of the trial. • N Engl J Med doi:10.1056/ NEJMoa2415948

> Tom Nolan, clinical editor, The BMJ, London; sessional GP, Surrey Cite this as: BMJ

2025;389:r601

clinical improvement. This case highlights that tinea incognito can mimic psoriasis, with or without nail damage, emphasising the importance of fungal cultures to avoid misdiagnosis.

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Patient consent obtained Cite this as: *BMJ* 2025;389:e082105

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MINERVA From the wider world of research

Mortality in surgery

More than 10 years ago, a survey in *The BMJ* drew attention to higher mortality in people who had elective surgical procedures carried out on Friday or over the weekend compared with Monday (*BMJ* doi:10.1136/bmj.f2424).

A study in Ontario, Canada, finds something similar. Among 400 000 patients undergoing 25

common procedures, adverse postoperative outcomes, including death, re-admission, and long and short term complications,

were 5% commoner in patients who underwent surgery on Fridays (*JAMA Netw Open* doi:10.1001/ jamanetworkopen.2024.58794).

Childhood mortality in low and middle income countries

An analysis of the age distribution of deaths in young children in 47 low and middle income countries finds that a disproportionately large number occurred in the early neonatal period (age <7 days) (*JAMA Pediatr* doi:10.1001/ jamapediatrics.2024.6908).

Early neonatal deaths are predominantly caused by conditions directly related to pregnancy and the perinatal period. Deaths later in childhood, in contrast, are mainly caused by infections and nutritional deficiencies. The implications—an urgent need for interventions to improve maternal and neonatal health care—are obvious.

Pandemic photographs

The New York Times marks the 5th anniversary of the pandemic with a collection of photographs that capture some of the weirdness and tragedy (www.nytimes. com/2025/03/10/world/asia/ covid-anniversary-photos.html).

Another piece in the same newspaper reminds us that, although we still don't know how the pandemic started, inquiry and debate about its possible origins have been stifled rather than encouraged (www.nytimes.com/2025/03/16/ opinion/covid-pandemic-lableak.html). Minerva was alarmed to learn that experiments with bat coronaviruses are still going on (*Cell* doi:10.1016/j. cell.2025.01.042).

Platelet rich plasma



Local injection of platelet rich plasma, prepared from the patient's own peripheral blood, is

sold as a way of promoting healing in injured tissue. Platelet derived growth factors are thought to enhance angiogenesis, cellular migration, and matrix deposition.

The important question, however, is not how intervention might work but whether it does. Evidence from randomised trials is mostly negative. In the treatment of greater trochanteric pain, for example, ultrasound guided, platelet rich plasma injections were no better than placebo (*J Bone Joint Surg Am* doi:10.2106/ JBJS.24.00763).

Microplastics

Last year a report that people with higher concentrations of plastic particles in arterial plaques were at increased risk of vascular events attracted a lot of attention (*N Engl J Med* doi:10.1056/ NEJMoa2309822). Many other studies claim to have found microplastics in human tissues.

A sceptical review in *Nature* points out that most of the studies are small and poorly controlled and that, since laboratories are hotspots of microplastic pollution, it's hard to rule out the possibility of contamination. So far, no convincing explanations of how plastics bypass biological barriers

have been forthcoming (*Nature* doi: 10.1038/d41586-025-00702-2).

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STATE OF THE ART REVIEW

Advances in the management of endometrial cancer

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Correspondence to: B R Corr Bradley.corr@cuanschutz.edu This is a summary of Clinical Review Advances in the management of endometrial cancer. The full version can be read here: https://www. bmj.com/content/388/bmj-2024-080978



The lifetime risk of developing endometrial cancer is 3.1%, and the overall five year survival rate is 81%.¹ The median age of diagnosis is 64; the disease is commonly found confined to the uterus owing to the early presenting symptom of postmenopausal bleeding. When localised disease is identified and surgically removed, five year survival rates reach 95%. However, five year survival rates for distant disease are only 18%. The three major treatment modalities for endometrial cancer remain surgery, radiation, and medical therapy. The most substantial advances are in the medical treatment options for endometrial cancers. Immunotherapy has had the greatest impact on treatment recommendations, but comprehension of tumour molecular profiles and targeted treatment responses have also enabled us to treat patients with the appropriate therapies.

WHAT YOU NEED TO KNOW

- Incidence rates of endometrial cancer are rising globally. It is the fourth most common cancer (behind breast, lung, and colorectal cancer) and the sixth most deadly cancer in women
- Treatment strategies have historically focused on a combination of surgery, radiation, and/or chemotherapy, based on the histology and extent of the tumour. Surgical removal of the tumour is the mainstay of treatment
- Advances in the evaluation and treatment of endometrial cancers are occurring at a rapid pace. Molecular classification is encouraged in all cases of endometrial carcinoma, to guide treatment and prognostic recommendations

Epidemiology

Uterine cancer is the fourth most common cancer in women (behind breast, lung, and colorectal cancer) and the sixth most deadly cancer in women. In people over 50 with an intact uterus, it is the second most common malignancy.³ In 2023 uterine cancer surpassed ovarian cancer as the most lethal gynaecological malignancy in the US.⁴

The incidence of endometrial cancer is increasing in the US and worldwide. Over the past two decades, the incidence has increased up to 20-fold across all age groups, and the disease is more prominent in Europe and North America than in lower income countries.⁵⁶

The reasons for these trends are multifactorial and not completely understood. More than 80% of endometrial cancers are oestrogen receptor positive and associated with oestrogen related risk factors such as obesity, nulliparity, late menopause, early menarche, and menopausal oestrogen supplementation.⁷ Changes in fertility and reproductive factors such as fewer pregnancies and nulliparity may contribute to the increase of endometrial cancer. Additionally, obesity is increasing worldwide and likely contributes to this trend. Other factors to consider include changes in perimenopausal hormone use, an increase in diabetes, a decrease in smoking prevalence, changes in contraceptive patterns, and changes in hysterectomy rates.⁶

Pre-invasive disease

Endometrial intraepithelial neoplasia (EIN) is a premalignant condition of the endometrium. The term EIN is defined as hyperplasia with atypia and replaced the previous classification system of endometrial hyperplasia that classified hyperplasia into four categories: simple or complex and with and without atypia. The risk of concurrent malignancy within the uterus and progression to malignancy varied widely between these categories from 1% for simple hyperplasia to 43% for complex hyperplasia with atypia.^{23 24} The development of endometrioid endometrial cancer is a stepwise progression from hyperplasia without atypia to hyperplasia with atypia to carcinoma. Unopposed oestrogen signalling has been implicated as a driver both in the development of EIN and in the progression of EIN to endometrioid endometrial cancer.

Management

Surgery

The standard of care treatment for EIN remains hysterectomy with consideration of bilateral salpingooophorectomy depending on menopausal status. However, given the rising obesity epidemic, particularly among younger people, and higher rates of delayed childbearing, fertility sparing options for this premalignant condition are of increasing interest.²⁵ Additionally, as the population ages and has higher rates of comorbid conditions, more patients will need non-surgical options. Finally, some patients may prefer non-surgical options.

Progestins

Progestins induce cellular differentiation and are an active hormonal intervention for treatment of EIN.²⁶ Given the relative rarity of patients who choose non-surgical management, neither the dose nor the schedule for progestin agents has been standardised in clinical management guidelines.

A meta-analysis of studies of progestin therapy for patients with EIN found that 86% achieve a complete response and 16% of responders ultimately have recurrence.³⁰ Body mass index <35 has been associated with a higher resolution rate in premenopausal patients with EIN receiving progestin therapy.³¹ In patients with endometrial cancer, body mass index <25, maintenance therapy, and pregnancy are all associated with improved long term oncological outcomes.²⁸

Non-surgical management options for EIN include treatment with progestin therapy, either with a levonorgestrel intrauterine device, oral progestins, intramuscular injections, or vaginal progestins. Side effects of oral progestins include weight gain, bloating, nausea, and venous thromboembolism.

On the basis of this side effect profile and difficulties with adhering to a daily regimen of oral medications, progestin-containing intrauterine devices have emerged as the non-surgical treatment of choice for EIN. In a series of more than 300 patients with atypical hyperplasia who received progestin in the form of an intrauterine device or orally, the regression rate was higher in patients receiving the intrauterine device (95%) than in those receiving oral progestins (84%).³³ A more recent prospective phase 2 study of an intrauterine device for 57 patients with endometrial cancer and atypical hyperplasia showed a response rate of 91% for atypical hyperplasia, with progression evident in 5.5% of patients.³⁴ An overall 9.5% relapse rate after initial response was also seen. The possibility of progression, as well as relapse, mandates the careful surveillance of patients selecting conservative management. This management consists of regular endometrial biopsies, generally every three to six months for the first one to two years. Response to hormonal therapy is expected to occur within six to 12 months after initiation, so lack of response on the three month biopsy is not rare. After childbearing is complete, we recommend surgery with completion hysterectomy, with or without bilateral salpingo-oophorectomy.

Novel therapies

Given that remission rates with progestin are less than 100%, pursuit of novel therapies to improve treatment of these lesions is needed. Metformin is a potential strategy as it has anti-proliferative effects and sensitises the endometrium to the effects of progestin. One pilot study randomised patients with EIN to metformin and megestrol acetate combined compared with megestrol acetate alone. The response rate to dual therapy was better, with a higher rate of complete response (75% v 25%) and fewer non-responders (25% v 50%); however, the results were not significant, potentially because of the small sample size of only 16 patients.³⁵ Recent in

vitro and in vivo evidence shows that the combination of metformin and a progestin has a synergistic effect, with the addition of metformin causing a greater suppressive effect on endometrial cancer cells than either metformin alone or progestin alone.³⁶ Multiple reviews suggest that metformin may play a role in improving response rates of EIN to progestin, but data are conflicting.^{37 38}

Molecular classification

Advances in molecular analysis and the development of novel therapeutics beyond cytotoxic chemotherapies have revolutionised the characterisation of and therapeutic strategies for endometrial cancer over the past decade. The analysis schema ProMisE (proactive molecular risk classifier for endometrial cancer) has been validated using a combination of immunohistochemistry and Sanger or next generation sequencing.¹⁷⁻⁴⁰ Each of these classifications carries with it a unique molecular profile (fig 1). However, that molecular markers exist beyond, and within, these classifications which have significant prognostic and therapeutic implications has become apparent.

Historically, risk factors for recurrence of endometrial cancer were commonly described as low risk, high risk, or high intermediate risk. These classifications arose from well studied risk factors such as tumour histology, tumour grade, tumour size, depth of myometrial invasion, and presence of lymphovascular space invasion.⁴²⁻⁴⁴ Treatment recommendations of observation, vaginal brachytherapy, whole pelvic radiation, chemotherapy, or a combination of these modalities have subsequently been evaluated in multiple phase 3 clinical trials on the basis of these well established risk factors.⁴⁴⁻⁵⁰

Molecular classification has progressed beyond being a solely prognostic indicator and is now an essential guide to treatment modalities in the adjuvant and recurrent disease setting. Examples include the adjuvant use of immune checkpoint blockade in stage III/IV and recurrent disease. However, ongoing clinical trials plan to expand our treatment recommendations on the basis of molecular profiles.

Endometrial cancer treatment

Surgery

Surgical removal of the primary tumour with a total hysterectomy and bilateral salpingo-oopherectomy continues to be the mainstay of treatment for endometrial cancer. A minimally invasive approach is recommended for presumed early stage disease.^{54 55}

Radiation

Adjuvant therapy

Use of radiation in endometrial cancer, including external beam radiation, vaginal and interstitial brachytherapy, and ablative radiation, has evolved on the basis of many clinical trials, including combinations with systemic therapy.



Fig 1 | TCGA/ProMise molecular classifications of endometrial cancer. DNA polymerase ϵ (POLE) pathogenic mutations are detected by next generation sequencing. Mismatch repair (MMR) and p53 status is determined by immunohistochemistry (IHC) staining. **Evaluation is performed** in order delineated. MMRd=mismatch repair deficient; NSMP=no specific molecular profile; p53abn=p53 abnormal

Combination therapies with chemotherapy have led to changes in more advanced disease. Molecular analysis indicates that specific subtypes benefit from different approaches.⁵⁸

Recurrent therapy

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Locally and regionally recurrent disease both heavily involve radiation in the unirradiated pelvis, and occasionally with previous external beam radiation. Improvement in radiation planning and delivery, as well as advances in interstitial brachytherapy, mean that most of these patients can be cured.⁶⁰ Image guided, volume directed brachytherapy has provided significant advances in multiple gynaecological cancers, including uterine cancer, and is now the standard of care in recurrent uterine cancer in the vaginal canal.⁶¹ Postoperative pelvic intensity modulated radiotherapy has become the standard of care for reduction of toxicity including gastrointestinal and bone marrow while maintaining effective outcomes.⁶²

Ablative radiation also plays a role in patients with limited site distant recurrence.⁶³

Identifying a subset of patients with limited local and/or regional recurrence outside of previous external beam fields may enable cure, and these patients without distant metastases should be identified for multidisciplinary input. Local recurrence alone should be treated with radiation in this setting, and systemic therapy may not offer additional substantial benefit. For regional recurrences, concurrent systemic therapy is more commonly preferred.

For oligometastatic disease, stereotactic body radiation therapy is an effective and well recognised approach for limited site recurrences. National Comprehensive Cancer Network (NCCN) guidelines on uterine cancer include this as a category 2B recommendation for one to five metastases with disease otherwise controlled, as well as an option for visceral disease such as liver metastases with systemic therapy.

Chemotherapy

Adjuvant therapy

Since the early 2000s chemotherapy has been the standard of care for women with advanced or recurrent endometrial cancer. Before the current regimen, the triplet of paclitaxel, adriamycin, and platinum based agents was the standard of care.⁶⁷ In 2010 a randomised controlled trial reported that the combination of carboplatin and paclitaxel was equally as effective as the triplet regimen.⁴⁸ Most notably, the addition of immunotherapy agents to adjuvant chemotherapy has changed the standard of care, and is discussed in detail in the immunotherapy section.

Recurrent therapy

In patients who progress after first line chemotherapy, no defined platinum-free interval or guidelines for when to re-treat with platinum based therapy exist, as they do for ovarian cancer. First line trials have allowed re-treatment after six to 12 months. This needs to be considered when prescribing second line therapy. Other options have not vielded significant outcomes and are often considered palliative. The two most active agents for treatment of recurrent disease are single agent doxorubicin and single agent paclitaxel dosed on a weekly regimen.⁶⁸⁻⁷⁰ These agents have been investigated in phase 2 trials of 43 and 30 patients, respectively, and found to have activity. Subsequent therapy options include multiple chemotherapy agents. Unfortunately, none of them is overtly effective and they are often given in a solely palliative setting.

Immunotherapy

The effectiveness of immunotherapy as second line therapy has led to investigations to move this treatment to frontline therapy. Given the efficacy of chemotherapy in inducing antigen presentation, priming tumour cells to become receptive to the immune attack triggered by checkpoint inhibitors in other tumour types, a similar strategy was tested in endometrial cancer.^{81 82} At 12 months, the progression-free survival was 74% among patients with mismatch repair deficiency receiving pembrolizumab and 38% among those receiving placebo (hazard ratio 0.30, 95% confidence interval 0.19 to 0.48).

Similarly, the benefit of dostarlimab was confirmed in a phase 3 randomised controlled trial comparing carboplatinpaclitaxel-dostarlimab with carboplatin-paclitaxel-placebo among patients with stage III and IV endometrial cancer. These studies show the benefit of checkpoint inhibition along with chemotherapy in improving progression-free survival, particularly for patients with mismatch repair deficient disease.

Targeted therapy

Targeted therapies in endometrial cancer range from use of broad spectrum agents in select populations, such as hormonal therapies in oestrogen receptor/progesterone receptor positive tumours, to directly targeting tumour antigens such as HER2 with monoclonal antibodies. With advances in drug development and molecular evaluation, multiple targets have been established.

Hormonal therapies

Chemotherapy is the standard of care for patients with advanced and recurrent disease. However, low grade tumours, which can account for up to 50% of recurrences, are less likely to respond to chemotherapy. In advanced stage or recurrent disease, response rates to hormonal therapy can be up to 55%.⁸³ Patients with oestrogen receptor/progesterone receptor positive tumours are more likely to respond to these therapies. For patients with advanced or recurrent tumours that are oestrogen receptor/ progesterone receptor positive, hormonal agents can be considered as first line therapy. This is supported by both NCCN and European Society for Medical Oncology (ESMO) guidelines,^{84,85} which recommend hormonal therapy for patients with recurrent, low grade endometrial cancer.

Progestins and aromatase inhibitors are commonly used as standard hormonal agents in the treatment of patients with low grade endometrial cancer. Response to progestin therapy is higher in progesterone receptor positive tumours with a well differentiated histology, and recurrence after progestins generally does not extend beyond the uterus. Use of progestin therapy has been further limited by the development of thromboembolic events.

Selective oestrogen receptor modulators, such as tamoxifen, are also suggested as an effective hormonal therapy for endometrial carcinoma. Although tamoxifen is not effective as a single agent, several studies have looked at the sequential use of tamoxifen and progestins.

Alternative selective oestrogen receptor degraders, such as fulvestrant, have also shown activity as a hormonal therapy for hormone receptor positive endometrial cancers.

Emerging therapies

PARP inhibition

Poly (ADP-ribose) polymerase (PARP) inhibition is a targeted strategy used as maintenance therapy in ovarian, breast, and prostate cancers and is most effective in a BRCA mutated or homologous recombination deficient patient population. Several hypotheses have suggested that alternative DNA damage pathways can lead to efficacy in endometrial cancers.

The combination of PARP inhibition and immunotherapy hypothesises that an accumulation of DNA damage caused by the PARP inhibitor may complement the immune checkpoint blockade.

HER2 targeted therapies

Recognised for its role in other solid tumours such as breast and gastroesophageal cancer, HER2 has gained attention as a predictive and prognostic biomarker in endometrial cancer.¹¹⁰ Existing studies and clinical trials have used both the ASCO/CAP breast and gastric scoring systems and found that rates of HER2 positivity approach 20-30% in uterine serous carcinoma.¹⁷⁻¹¹³ HER2 is also expressed and amplified in uterine carcinosarcoma as well as in the more common endometrioid carcinoma.^{114 115}

Antibody-drug conjugates (ADCs) directed at HER2 have quickly gained traction in the treatment of recurrent HER2 positive endometrial cancer. ADCs have the benefit of more directed tumour cell kill with minimisation of side effects compared with conventional chemotherapy.

Antibody-drug conjugates

ADCs are a novel therapeutic class used across many tumour types. In gynaecological cancers, their approvals have been limited to ovarian and cervical cancers, but significant evaluations in endometrial cancer are under way. Not all ADCs are the same. ADCs have three main components, and variation in any one has the potential to affect response. The three components are the antibody, the linker, and the payload. We commonly classify them on the basis of target antigen. The ADCs furthest advanced in evaluation and use in endometrial cancer are those targeting the HER2 antigen as discussed above. TROP2 is another target antigen with recent publication of results specific to endometrial cancer. Other agents targeting highly expressed target antigens such as folate receptor α (FR α) and B7-H4 are also under investigation.

Guidelines

The impact of molecular analysis on prognosis and therapy indications has reached a point of shift into the global staging and treatment of endometrial cancers. The European Society of Gynaecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO), European Society of Pathology (ESP), International Federation of Gynecology and Obstetrics (FIGO), and the NCCN have each incorporated molecular analysis into updated staging and guidelines in 2021 and 2023.⁸⁴⁻¹²² In 2021 ESGO, ESTRO, and the ESP jointly produced updated management guidelines re-categorise the risk groups into low, intermediate, high-intermediate, and high on the basis of a combination of histopathological risk factors and molecular classifications.

Competing interests: See bmj.com.

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NIHR ALERTS

Schoolchildren with asthma face different risks at different ages

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Influence of age on clinical characteristics, pharmacological management, and exacerbations in children with asthma

Khalaf Z, Bush A, Saglani S, et al Thorax 2024;79:112-119

Why was the study needed?

More than 1 million children are being treated for asthma in the UK. The main treatments are short-acting relievers, which open airways and relieve asthma attacks; and long-acting preventers, which reduce inflammation in the lungs and prevent attacks.

Asthma is treated differently in children aged 1 to 5 years compared with older children. British Thoracic Society guidelines separate

What did the study do?

Researchers analysed the medical records of 119611 children with asthma in England from 2004 to 2021. The study looked at how asthma and related conditions changed with age, including how

children aged 5 to 11 years from adolescents. However, until a recent update, National Institute for Health and Care Excellence (NICE) guidelines on the management of asthma were similar for younger (5 to 11 years) and older children (12 to 16 years). These age groups are considered separately in the updated version as older children are included alongside adults.

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Health and Care Research

likely participants were to have an asthma attack or to have a delayed diagnosis.

What did it find?

The study found that:

- Children aged 5 to 8 years were most likely to have an asthma attack (14% of these children had an attack in every whole year, compared with 7% among those aged 12 to 16 years)
- Delayed diagnosis was most common in the youngest children
- Young people aged 12 to 16 years were least likely to receive both long-acting preventers and short-acting relievers; 1 in 5 used short-acting relievers only for two years.

For children of all ages, being from a more deprived area and having a delayed diagnosis increased the risk of an asthma attack. Other risk

Why is this important?

The findings imply that childhood asthma could be diagnosed and managed more effectively. Better understanding of the impact of age could increase diagnoses and improve treatment choices for all. For example, younger children might need more help preventing asthma attacks.

Young people aged 12 to 16 years might need a medicine review to ensure they are using both short-acting relievers and long-acting preventers. Some might also benefit from help with weight management because being overweight can increase the chance of an asthma attack. Fewer than half (40%) of the children had a recorded body mass index

What's next?

Updated NICE guidelines on the management of asthma now consider children aged 5 to 11 years separately from those aged 12 and above.

British Thoracic Society guidelines issued in 2016 stated that people using short-acting relievers regularly should also use long-acting preventers. One approach to this is known as maintenance and reliever therapy (MART); this was recommended to adults with a history of asthma factors varied with age. Compared with the other age groups:

- Children aged 5 to 8 years were more likely to have an asthma attack if they were male, or had eczema or food and drug allergies
- Those aged 9 and above were more likely to have an asthma attack if they were obese or allergic to air particles.

In further research among children with asthma, the same team found that less than half received the recommended asthma reviews, inhaler technique checks, and asthma management plans. Children who received all of these interventions had a reduced chance of an asthma exacerbation (reduction of approximately 30% in 12 months).

(BMI) in this study; the researchers call for BMIs to be recorded routinely in asthma consultations.

In all ages, delayed diagnoses were linked with asthma attacks, but this was particularly common in the youngest group. Early diagnosis gives children access to annual reviews, an asthma management plan, and resources to learn about their condition.

British Thoracic Society guidelines on the management of asthma were updated in 2016. In this long-term study, most data were from before 2016, which could explain why some children received short-acting relievers only for extended periods. This is no longer recommended.

attacks on medium dose inhaled corticosteroid. It is now recommended as part of the treatment pathway in the 2024 NICE guidelines for children aged 5 years and older. However, MART is not licensed for children under 12 years old so this use would be off-label. The researchers call for trials to test its safety and effectiveness in younger children. They also call for trials to consider narrower age categories for children with asthma.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. Further details of other interests, disclaimers, and permissions can be found on bmj.com Cite this as: *BMJ* 2025;388:q2534



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PRACTICE POINTER

Caring for patients experiencing homelessness

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There has been a worldwide rise in homelessness over the past 10 years.¹ On a single night in 2024 roughly 771 480 people in the United States were experiencing homelessness, the highest figure since reporting began in 2007.² Equivalent figures in England showed that, on a given night in 2024, an estimated 354 016 people were homeless, which is 1 in 160 people.³

Health and homelessness are closely interconnected, and there is much that can be done by healthcare professionals to improve the lives of people experiencing homelessness. Here, we explore the health impacts of homelessness and barriers to accessing healthcare, with a focus on adults in high income countries. We also offer practical considerations for clinicians providing care to people experiencing homelessness.

How does homelessness affect health?

Patterns of homelessness are complex and diverse and include rough sleeping; staying in temporary accommodation such as night shelters, hostels, and women's refuges; and hidden forms of homelessness such as staying with friends, sofa surfing, and living in squats or "beds in sheds."⁴ The support needs of people experiencing homelessness are also diverse. A person who has become homeless due to a job loss but without other risk factors may require little support and be able to return to housing quickly. For many, however, homelessness can be a longer term problem, resulting from an accumulation of risks and traumatic experiences at different points along their life course.⁵

The landmark Marmot Review in 2010 drew widespread attention to the inequalities across socioeconomic groups in the UK, showing that lower socioeconomic positions were associated with worse health.⁶ More recently, a systematic review and a cross-



sectional study have compared health outcomes in homeless populations against the housed population and describe marked differences.^{7 8} In the UK, the average age of death for the homeless population is around 30 years lower than for the general population.⁹ A population based, cross-sectional study of linked hospitalisation and mortality data in England has estimated that 30% of these premature deaths are due to causes amenable to timely and effective health care.¹⁰

Recent systematic review data have shown that people experiencing homelessness perceive significant stigma and discrimination from healthcare professionals.¹¹ Inadequate understanding of the underlying causes of homelessness by healthcare professionals means that individual choices are often blamed¹² despite robust research illustrating the complex interaction between the structural, economic, and individual factors involved, many of which are outside the control of those affected (see box 1).¹³ Homelessness typically represents only one indicator of social exclusion, intersecting with multiple different forms of marginalisation. This is relevant for clinicians because it is not only the lack of housing that affects a person's health needs. Other aspects of social exclusion may precede or occur because of homelessness. For example, a history of childhood trauma or substance use disorder may have a more profound or immediate effect on health needs than homelessness itself.

What are the barriers to healthcare?

People experiencing homelessness commonly encounter multiple difficulties accessing and using health care. Active removal of these barriers by clinicians is needed to improve the accessibility and quality of services.

A systematic review of homeless persons' experiences, with data mostly from the US and Canada, described individuals not feeling welcome or cared for when seeking medical attention, feeling labelled and stigmatised, and being treated with a lack of respect and empathy.¹⁷ Internalised barriers among people experiencing homelessness are also recognised. Individuals may develop a presumption of their own poor health or early death, resulting in an ambivalence towards addressing their health issues, an expectation of rejection from services, or a feeling of embarrassment about personal hygiene that restricts confidence when accessing care.¹⁸ Resulting patterns of healthcare use include late presentation of illness (often when a crisis point is reached), increased rates of missed

WHAT YOU NEED TO KNOW

- People experiencing homelessness face multiple barriers to accessing health care and have high mortality and morbidity from preventable or treatable conditions
- Clinicians should consider preventive care, harm reduction, and the increased rates of multimorbidity and early onset frailty when caring for people experiencing homelessness
- Trauma informed practice provides a framework to enable respectful, safe, collaborative, and empowering relationships

Box 1 | Causes and impacts of homelessness in high income countries $^{78\,10\,13\cdot16}$

Underlying causes of homelessness

Structural, societal, and economic factors:

- Poverty and inadequate social security benefits
- Unaffordable housing
- Unemployment
- Social exclusion
- Discrimination
- Unmet health and social care needs
- Individual factors:
- Adverse childhood experiences
- Mental health problems
- Drug and alcohol misuse
- Poor physical health
- Experience of the care system as a child
- Experience of the criminal justice system
- Experience of migration and seeking asylum
- Loss of work or benefits

- Neurodiversity
- Brain injury
- Death of a family member
- Relationship breakdown
- Experience of violence
- Experience of domestic abuse
- Lack of social support networks
- Impacts of homelessness
- Stigma and discrimination
- Increased mental ill health including substance misuse and dependency
- Higher rates of self harm and suicide
- Increased use of acute hospital and emergency care
- Increased risk of TB, hepatitis C, HIV
- Increased risk of physical long term conditions including epilepsy, asthma, COPD, and cardiovascular disease
- Premature deaths from preventable and treatable conditions (average age of death 30 years below that of the general population)

Box 2 | Examples of how to apply the principles of trauma informed practice in consultations $^{\rm 24}$

Consider safety

- Ensure physical, emotional, and social safety. Ask "Are you safe?" or "What would help you to feel safe?"
- Avoid re-traumatisation, for example, avoiding redundant repetition of potentially distressing aspects of a person's history

Collaboration and choice

- Ask the person experiencing homelessness what their priorities are and what support they want: "I won't tell you what to do"
- Explain choices clearly and transparently: "There are some options.... What do you think?"

Establish trust

- Practice authentic empathy
- Be positive and supportive, not just with words but with body language and, where possible, the environment

Empowerment

- Understand that someone who has experienced trauma may feel powerless and have low self worth: support them to make decisions and to act on them
- Validate the patient's experience: "Thanks for telling me. I have some sense of how difficult that was for you. It helps me when trying to think through the best support that we can offer"

appointments, self discharge before treatment is complete, and an increased use of emergency and acute secondary care rather than primary care services.¹⁴¹⁹

Administrative barriers can also contribute. Volunteers with lived experience in a 2024 mystery shopper study attended 13 London GP surgeries to request an appointment for a problem requiring urgent medical attention.²⁰ Over half of the visits ended with refusal to register the person, most of which were wrongly based on the person's inability to provide proof of identification or address. Hospital discharge processes have also

been shown to have considerable impact on people experiencing homelessness.²¹ Healthcare professionals working in mainstream and specialist inclusion health services report that people experiencing homelessness are discharged from hospital with unmet health needs often or all of the time.¹² Almost half of the people experiencing homelessness in the same study who had been admitted to hospital were discharged either to the streets or to unsuitable accommodation. Problems with discharge letters and poor communication between services have also been linked to patients losing access to care and falling through gaps in the system.²¹

Practical considerations for clinicians providing care to people experiencing homelessness

Encounters with healthcare professionals can have a profound impact when a person is experiencing homelessness.¹⁷ Fortunately, there is now a wealth of research evidence and guidelines¹⁴ to inform best practice.

Trauma informed practice (TIP)

Psychological trauma and homelessness are closely interlinked. A recent systematic review of adults experiencing homelessness in the US, Canada, and UK showed that the lifetime prevalence of one or more adverse childhood experiences was 89.8%.²² Trauma also often happens as a result of homelessness—for example, experiencing or witnessing violence or sexual assault.²³

Trauma informed practice is an approach grounded in an understanding of how exposure to trauma affects an individual's neurological, biological, psychological, and social development (box 2).²⁴ Clinicians practising this approach will recognise how trauma can affect a patient, their ability to feel safe, their behaviour, and their engagement. TIP allows for prioritisation of the patient's physical and psychological safety while avoiding re-traumatisation. Establishing trust, allowing choice, collaboration, and empowerment are key.²⁵

Prescribing

Explore a patient's social context when creating shared management plans adapted to their living conditions. Patients may not be able to safely store medication if sleeping rough, sofa surfing, or in accommodation projects without locked safes, and so could benefit from weekly or even daily dispensing. Similarly, taking medication four times a day may not be achievable for a person managing challenging life circumstances, so consider whether a more appropriate regimen can be prescribed.

Further considerations may include:

- If a medication should be taken with food, alternatives may need to be considered for patients who don't have regular, easy access to meals
- Home oxygen may not be safe if a patient is living in a hostel in proximity with people smoking tobacco or other drugs

the**bmj** Visual summary 🐠

Patients experiencing homelessness

Improving access to healthcare

People experiencing homelessness commonly face multiple barriers to accessing and using health care. This graphic explains practical considerations for clinicians providing care to people experiencing homelessness which can be used to improve the accessibility and quality of services.



PATIENTS' PERSPECTIVE

"The sores on my leg were getting worse, the smell of rotten flesh followed me, I was 25 and fearful that, with repeated injecting, I was going to lose my leg. I could not face another trip to A&E no matter what support the hostel workers tried to give me. Years on the streets and repeated negative encounters with medical professionals made me fear going.

"A drop-in I visited occasionally for a shower and to use their phone had a nurse visit a few days a week. Slowly, with chats over coffee in the building, I began to trust a health professional. It took a while, but she supported me to hospital, attending the appointment with me to get the treatment I needed. From this, I began to engage with other services, reassured that not all professionals have such negative attitudes.

"I now work in recovery helping others."

Tracey

"I was lucky, some people do not make it this far. I had the right interventions, at the right time, with the right level of support from my own GP. I used to hide from the world, and my health issues held me back: today, I fight each day to help others, to make positive changes for those homeless, whose health is affected by this."

Majid

- If a medication requires refrigerator storage (such as insulin), ascertain whether a refrigerator is accessible. If not, you may need to consider how this can be safely stored, as well as your advocacy role in securing accommodation
- If a medication may require easy access to bathrooms (such as diuretics or bowel preparation), ascertain the accessibility of appropriate facilities
- If a medication has sedating effects, discuss safety with a patient who may be sleeping in risky places.

Prevention

As people experiencing homelessness have more limited access to primary and preventive health care, use any contact as an opportunity for preventive care. This could include: screening for bloodborne viruses, sexually transmitted infections, hypertension, and diabetes; giving vaccinations; smoking cessation and nutrition advice; referral to drug and alcohol recovery services.¹⁴

Clinicians can also use a harm reduction approach where possible. This may include street drug overdose prevention planning, education about safer injection practices, opioid substitution treatment, and mental healthcare safety planning.²⁶ These offers of input need to ensure collaboration with the patient at all times, so that you are working at a pace where the patient's priorities for care take precedence and they do not feel overwhelmed.²⁴

Long term conditions and frailty

People experiencing homelessness have higher rates of long term conditions and multimorbidity than the general population, so require comprehensive



assessment to identify health issues and timely communication with other services (see box 1).⁷ Frailty and age related conditions (particularly cognitive impairment) may present earlier and at higher rates in people experiencing homelessness. Comparisons have shown that people experiencing homelessness who are in their 40s and 50s have similar frailty scores as housed individuals in their 70s and 80s.²⁷ Be conscious therefore that screening for cognitive impairment, frailty, and access to support and services usually directed at older people may be appropriate at a much younger age.

Inclusive design of primary care services

Dedicated primary care centres for people experiencing homelessness do exist in many cities and allow the delivery of flexible, holistic, integrated care.²⁸ These services may be viable only in locations with large numbers of people experiencing homelessness, but they can serve as models for trauma-informed service design. Examples include providing flexibility with appointments, drop-in services, longer appointment times, and close partnership working with local hospitals and community homeless services. Specialist services also demonstrate inclusive registration policies that don't discriminate against people without an address, a key policy that should be applied by all primary care services.¹⁴

Research and guidance are increasingly showing the value of involving people with lived experience of social exclusion in developing and improving services.²⁹ Co-designing services with people with experience of homelessness can assist with removing many of the barriers in access to care.

Safe discharge from hospital³⁰³¹

An admission to hospital can be a vital opportunity to address the health and social needs of a person experiencing homelessness, to ensure they have the necessary support in the community on discharge and reduce the risk of readmission. Involve the person experiencing homelessness in decisions about their discharge and aim to confirm plans as far in advance as possible. Audit of discharges can be a useful tool to improve quality of care.

Key discharge considerations include:

- Communicate with housing providers—Patients experiencing homelessness or at risk of becoming homeless should be identified as soon as possible on admission to hospital. If they don't have anywhere safe to stay on discharge, seek their consent to make a referral to the local housing authority. In England, this is a statutory requirement for hospital trusts under the Homelessness Reduction Act 2017. If the patient is being discharged to temporary accommodation such as a hostel, it is important to liaise with the service before discharge to agree discharge plans and establish whether their ongoing care needs can safely be provided in that setting. Otherwise, you may need to consider a local intermediate care pathway (if available) or liaise with other professionals in the community to facilitate a safe discharge.
- Avoid unmanaged self discharge—On admission, aim to understand vulnerabilities that may put a patient at risk of self discharge, such as drug and alcohol dependence. If necessary, follow hospital protocols for management of withdrawal. Support from a keyworker or peer advocate can help enable the patient to engage with treatment during an admission. If mitigating steps have failed and a self discharge cannot be avoided, ensure that the community services supporting the patient have been informed and that discharge details are communicated to their GP.
- *Involving relevant partners and services*—Work with the patient to identify professionals who may be involved in their care and can support discharge planning and ensure that they are registered with a GP service on discharge. If there are any safeguarding concerns, a referral to the local safeguarding team should be considered. Specialist multidisciplinary in-reach teams or pathway teams have been established internationally to support homeless patients in hospital and to coordinate their discharge planning.

Advocacy

At an individual level, clinicians can use every contact as an opportunity to address their patient's social needs. This could involve onward referrals; for example, to housing or alcohol and drug recovery services or providing evidence to help with a housing application. A short letter setting out any health problems or disabilities, how the condition affects the patient, and how being homeless could affect their vulnerability can help a council to decide if the patient has a priority need for housing. Beyond individual advocacy, clinicians can also use their position to advocate at a broader level and help change structures and policies contributing to the rise in homelessness. This could involve joining campaigns, writing to politicians, and educating other healthcare professionals about care for people affected by homelessness, poverty, and social exclusion.

We acknowledge the survivorship of the people experiencing homelessness who we meet and represent in our work. They continue to be an inspiration through their resilience and strength in the face of adversity.

Contributors: GA conceived the article and wrote the initial draft, which was revised and approved by AEW, MP, and SWH. GA, AEW, and SWH are guarantors. MP was the contact for patient involvement. The authors thank the patients who contributed their personal stories but wish to remain anonymous.

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HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

One of the authors, MP, has lived experience of homelessness and works for Pathway as the Lived Experience Programme Manager. She has provided the personal insights and perspectives included in this article from her own experiences and those of colleagues with lived experience. Patient perspectives have been given pseudonyms to maintain anonymity. MP's opinion was sought on what should and shouldn't be included in the article, and she was involved in revision and editing.

EDUCATION INTO PRACTICE

- How does your experience of providing care for people experiencing homelessness accord with the information in this article? Are there any aspects that feel particularly pertinent to you?
- Are there any changes you might consider making in your communication or consultations with people experiencing homelessness?
- What changes could you make to the organisation of your service to reduce barriers to access for people experiencing homelessness?

ADDITIONAL EDUCATIONAL RESOURCES FOR HEALTHCARE PROFESSIONALS

- National Institute for Health and Care Excellence. Integrated health and social care for people experiencing homelessness (NICE guideline NG214). 2022. https://www.nice.org.uk/guidance/ng214
- Ward A, Andrews L, Black A, Williamson AE. Communicating effectively with inclusion health populations: 2022 ICCH symposium. *Patient Educ Couns* 2023;117:107977
- Pathway—Homeless and inclusion health charity. https://www.pathway.org.uk/
- National Health Care for the Homeless Council. https://nhchc.org/clinical-practice/
- Pottie K, Kendall CE, Aubry T, et al. Clinical guideline for homeless and vulnerably housed people, and people with lived homelessness experience. CMAJ 2020;192:E240-4

WHAT YOUR PATIENT IS THINKING

Finding the right treatment for severe depression



Tony Frais found himself unprepared for the diagnosis of severe depression, and for the challenge of trying different treatments

aking in the middle of a dream, I felt a palpable click in my brain. Suddenly I felt verv unwell. It was the same uncomfortable feeling you get when you are on the downhill part of a roller coaster. I got out of bed very scared of what was happening to me. I decided to book an appointment with my GP. My expectation was that I would be prescribed a pill and that would be the end of my discomfort. It never crossed my mind that any of this would be related to my mental health. I had no symptoms or concerns before this.

My GP referred me to a psychiatrist. It was an evening appointment, and I turned up feeling quite cheerful. Unknown to me at that time, I was experiencing a feature of severe depression known as diurnal variation. I felt unwell for most of the day, and then magically the symptoms disappeared in the evening, before returning the next day.

Treatment with a positive thought

I was prescribed medication to help my mood and sleep, but it didn't make me feel any better. I then tried another medication that didn't help. Nothing seemed to be working. My hope for recovery was fading fast. This led to thoughts of suicide. In desperation, and believing there was nothing to lose, I started looking on the internet for other treatment options. I discovered electroconvulsive therapy and asked to try it. I had a full course of treatment.

After a few weeks I walked outside and remarked to myself,

WHAT YOU NEED TO KNOW

- Severe depression can appear from nowhere with no previous symptoms, leaving patients confused, frightened, and lost
- When discussing a diagnosis of severe depression, help the person to understand that treatment may be complex and that it might take time to find the right approach
- Having an open conversation about the potential for relapse can help patients understand the importance of continuing treatment

EDUCATION IN PRACTICE

- How could you ensure that a person with severe depression feels supported to navigate different treatment options?
- When might you have a conversation about relapse and the importance of continuing treatment?



"What a lovely sunny day." The symptoms had disappeared. It felt as though my brain had recognised that I had not had a positive thought like that for 10 months. The depression went as quickly as it came.

Finding the right support

My focus now is on preventing relapses. I recognise that psychotherapy is crucial to this. Finding a psychotherapist who tailored the treatment to my needs and was on the same wavelength as me was challenging. Not getting anywhere with my first psychotherapist, I started to think that this kind of treatment might be a waste of time. But I tried two other psychotherapists before I eventually found the right person, and they were extremely helpful and effective in supporting me to recognise possible relapses. I wish I had

been told at the beginning of my journey that I might need to try a few different therapists before finding the right one.

Alongside my psychotherapy I have remained on medication for the past 20 years. I have no serious side effects and would worry about another relapse if I were to come off it. I was not aware that the dysregulation in my brain caused by the depression meant there would be the ever-present potential of relapse. I wish someone had told me that recovery from depression is fragile, that there may be relapses, and that I would need to manage them. Knowing this would have helped me to recognise the importance of continuing treatment and leaning on the support I need to help me avoid the drop of a roller coaster again.

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INSWers

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CASE REVIEW Unilateral decreased vision and macular lesions in a boy

the evidence for this is limited. supplements might help reduce the risk of early

and choroidal neovascularisation indicate a , srasse, macular holes, macular scars, sontinuity, increased macular thickness, a large thickness retinal damage, interruption of toveal their vision has improved. However, tull the retinal structure has been restored and that their vision is stable. For some patients, zone, could persist even if the patient reports of the outer retina, especially the ellipsoid damage to the photoreceptors. Disruptions tissues, especially with a green laser, causing lipotuscin, which absorb more light than other of the laser. The fovea is rich in melanin and duration of application, and direction of focus 'iəmod indino 'dignalevew əhi no spuədəb closely related to the degree of injury, which The prognosis of laser induced retinopathy is 3 What factors might indicate poor prognosis?

1 What is the most likely diagnosis?

•ainsodxa degrees of injury to retina tissues from laser light Laser induced retinopathy: a condition of various

and may contribute to diagnostic difficulty. multiple short exposures at different times, and with laser injuries. This could be the result of stnate point patchy injuries seen in most patients on the macula, rather than the conventional In this case, disseminated lesions were visible

In addition, oral vitamins and antioxidant aware of the potential adverse effects of steroids. remains controversial and it is important to be in the treatment of laser induced retinopathy However, the role of systemic corticosteroids .sesso emos ni besu need zañ noitammaltni Systemic corticosteroid treatment for pathological growth of the choriocapillaris). especially choroidal neovascularisation (a to observe for development of complications, qu-wollot regular is regular follow-up 2 What is the management of this condition?

lesions involving the fovea and juxtafoveal area in the left eye (figure). Optical coherence tomography angiography revealed multifocal, spotted lesions corresponding to the lesions seen on fundus colour photography and disruption of the external outer photoreceptor ellipsoid, external

showed multifocal, yellowish, faceted

iuxtafoveal area

Parental consent obtained. Cite this as: BMJ 2025;389:bmj.2024-082355

Submitted by Min Ding, Qingjiong Zhang, and Wenmin Sun

- 2 What is the management of this condition? 3 What factors might indicate poor prognosis?
- 1 What is the most likely diagnosis?

limiting membrane, and retinal pigment epithelium.

A child was found to have noticeably decreased vision in his left eye during a routine optometry examination after showing normal vision six months previously. He did not self-report any eye symptoms (such as redness, pain, or tearing), headache, or dizziness, and had no personal or family history of eye diseases or other medical conditions. His parents reported that a green laser pointer (wavelength 532 ±10 nm, maximum output power < 50mW. Class III) had been purchased six months previously and the patient had been playing with it frequently. The patient reported looking directly at the laser pointer light on several occasions. He did not report that anyone else had shone the laser into his eyes. There was no history of trauma to either eye.

On examination, his best corrected visual

acuity was 20/32 in the left eye and 20/20

in the right eye. Fundus colour photography

See bmj.com.

PATIENT OUTCOME

associated with lasers.

be advised of the risks

• Parents and children should

indicate a poor prognosis.

thickness, large damage

range, and neovascularisation

สลิตรูร์ เทราอุรธราวที่ เจริธตรม

such as full thickness retinal

extent of injury, but factors

central black spot, or both.

common symptoms being

to laser light, with the most

injury caused by exposure

by various degrees of retinal

is a condition characterised

Laser induced retinopathy

LEARNING POINTS

painless decrease in vision or

Prognosis depends on the

Fundus colour photography shows multifocal, vellowish, faceted lesions involving the fovea and

boor prognosis.

ENDGAMES

CASE REVIEW

Unilateral decreased vision and macular lesions in a boy

