

CPD study pack

September 2018;262(1818)

The study pack contains this month's CPD exercise plus all relevant articles:

- Diagnosis and management of sleep-related epilepsy
- Tackling medication overuse headache in primary care
- GPs play a vital role in juvenile idiopathic arthritis

Fillable PDF templates*

- CPD exercise is a fillable PDF

CPD prompt and framework templates

- Journal article ● Case review ● Audit

* Adobe reader app needed for ipad etc
Rich text formatting enabled. Right click with mouse
for text style on desk top

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Practitioner CPD exercise

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Show impact

- Collection of data
- Practice audit to show improved care
- Case studies
- Implement a protocol
- Prescribing review
- Educational meetings
- Significant event audit
- Practice meeting
- Implement a new service
- Take on new role
- Significant event audits
- Change with feedback from patients and/or colleagues

Further options for sessional GPs

- Self audit of own practice:
 - Record-keeping
 - Referrals for investigations
 - Prospective condition based reviews
 - Random case analysis with colleagues
 - Review of telephone triage outcomes
- Update drugs in emergency bag

CPD Framework

Online all articles are associated with CPD prompts to written reflection in the form of three PDF fillable templates:

- Article review framework
- Case review framework
- Audit framework

SLEEP-RELATED EPILEPSY

1 Which of the following are characteristic of sleep-related hypermotor epilepsy (SHE)?

- A** The patient can recall the event afterwards
- B** Age of onset is generally 50 years or older
- C** The events have rapid onset and rapid offset
- D** The patient is capable of complex interactive speech
- E** The eyes are open

2 Which of the statements about SHE are true?

- A** Patients experience 1-2 events per night
True ☐ False ☐
- B** Clustering is common
True ☐ False ☐
- C** Events generally last 1-2 minutes
True ☐ False ☐
- D** Events can occur during daytime naps
True ☐ False ☐
- E** Patients may complain of excessive daytime sleepiness
True ☐ False ☐

3 Complete the statement:

Seizures in SHE are

,

seizures and therefore they involve no loss of

They may be preceded by

4 List any changes to your clinical practice that you may make having read this article.

MEDICATION OVERUSE HEADACHE (MOH)

5 Which of the statements are true?

- A** MOH does not occur in cluster headache unless there is associated migraine
True ☐ False ☐
- B** Prednisolone may aid medication withdrawal
True ☐ False ☐
- C** Headache does not always improve with medication withdrawal
True ☐ False ☐
- D** In the majority of cases MOH is a complication of migraine
True ☐ False ☐
- E** Paracetamol used once daily is sufficient to cause MOH, but paracetamol used 4 times a day 10 days per month is not
True ☐ False ☐

6 List three situations where a patient with MOH should be referred to neurology or a specialist headache clinic.

7 Complete the statement:

A good rule of thumb is to limit acute treatment to

days per

in patients with migraine and

This rule does not apply to patients with

headache.

8 List any changes to your clinical practice that you may make having read this article.

JUVENILE IDIOPATHIC ARTHRITIS (JIA)

9 Which of the statements are true?

A JIA is a clinical diagnosis

True ☐ False ☐

B It is more common in boys than girls

True ☐ False ☐

C Uveitis may precede the onset of arthritis

True ☐ False ☐

D Axial arthritis is common in children with enthesitis-related JIA

True ☐ False ☐

10 Complete the statement.

Systemic onset JIA is

and

distinct from other JIA subtypes. Prolonged

is a hallmark of the disease and classically follows a

pattern. The fevers are almost always accompanied by a

11 Patients with psoriatic arthritis have arthritis and psoriasis, or arthritis with at least two other features. List these features.

12 List any changes to your clinical practice that you may make having read this article.

Answers

SLEEP-RELATED EPILEPSY

1 A, C, E

2 A False (3-8 or more) B True C True D True E True

3 Simple, partial, partial, consciousness, an aura

MEDICATION OVERUSE HEADACHE (MOH)

5 A True B False C True D True E True

6 Appropriate management of MOH has not been successful; advice is required about management of the underlying primary headache disorder; there is concern that there may be an underlying sinister cause

7 Two; week; tension type headache; cluster

JUVENILE IDIOPATHIC ARTHRITIS (JIA)

9 A True B False C True D True

10 A Genetically; physiologically; fever; quotidian; rash

11 Dactylitis; nail pitting or onycholysis; psoriasis in a first-degree relative

Diagnosis and management of sleep-related epilepsy in adults

Mbizvo GK, Derry C. Diagnosis and management of sleep-related epilepsy in adults.

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Dr Gashirai K Mbizvo
MBChB (Hons)
MRes (Dis) MRCP
Clinical Research Fellow,
Centre for Clinical Brain Sciences and Muir Maxwell Epilepsy Centre,
University of Edinburgh, Edinburgh, UK

Dr Chris Derry
BSc MB BS MRCP PhD
Consultant Neurologist,
Department of Clinical Neurosciences and Sleep Medicine,
Centre for Clinical Brain Sciences,
University of Edinburgh, Edinburgh, UK



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Diagnosis and management of sleep-related epilepsy in adults

AUTHORS
Dr Gashirai K Mbizvo

MBChB (Hons)
MRes (Dis) MRCP
Clinical Research Fellow,
Centre for Clinical Brain
Sciences and Muir
Maxwell Epilepsy Centre,
University of Edinburgh,
Edinburgh, UK

Dr Chris Derry

BSc MB BS MRCP PhD
Consultant Neurologist,
Department of Clinical
Neurosciences and Sleep
Medicine, Centre for
Clinical Brain Sciences,
University of Edinburgh,
Edinburgh, UK

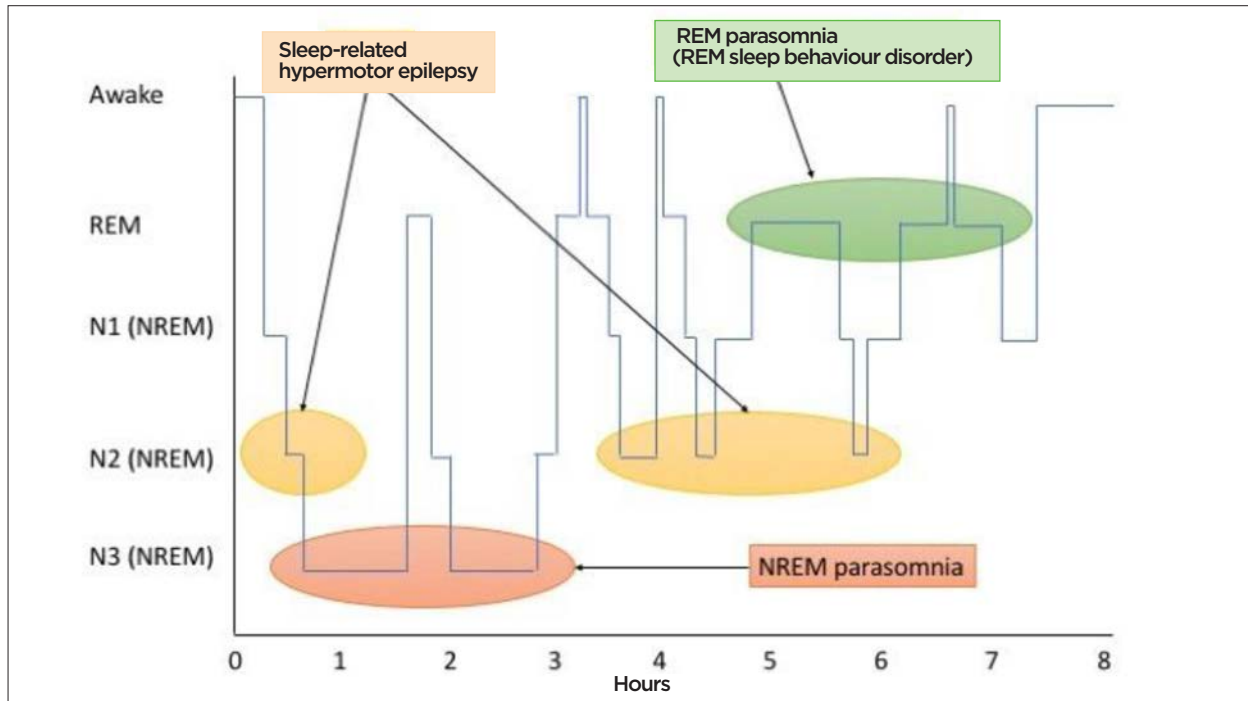


FIGURE 1

Hypnogram showing normal sleep architecture and associated nocturnal epilepsy/parasomnias. Sleep is divided into 90-120 min cycles consisting of two stages: non-rapid eye movement (NREM), and rapid eye movement (REM). NREM consists of three stages; in order of increasing depth of sleep, these are labelled N1, N2, and N3. We spend little time in N1 (5-10% or less of total sleep time). N2 occurs throughout the night (45-55% of total sleep time), but particularly within the first 30 minutes of sleep or shortly before waking. N3 (also called slow-wave sleep) occurs during the first third of the night, usually around an hour or more after sleep onset, and accounts for 10-20% of total sleep time. REM occurs predominantly during the final third of sleep and accounts for 18-23% of total sleep time. It is typically associated with vivid dreaming. REM is characterised by voluntary muscle atonia, except the extraocular muscles and diaphragm, and this is mediated by the basal ganglia⁴

What are the differential diagnoses?



EPILEPSY USUALLY PRESENTS WITH SEIZURES OCCURRING DURING BOTH WAKEFULNESS AND SLEEP. WHEN SEIZURES

occur exclusively or predominantly (more than 90%) during sleep, this is termed nocturnal epilepsy.¹

Nocturnal epilepsies account for 10-15% of all epilepsies,² and 80% of nocturnal epilepsies in adults are focal.³ They present a diagnostic challenge as they can be difficult to differentiate from normal movements and behaviour during sleep and also from several non-epileptic, sleep-related, motor and behavioural disorders.

This article largely focuses on sleep-related hypermotor epilepsy (SHE),

How should patients be examined and assessed?

previously called nocturnal frontal lobe epilepsy (NFLE), as this is not an uncommon presentation of nocturnal epilepsy yet it is often misdiagnosed as a non-epileptic sleep disorder, such as a parasomnia.^{4,5} Nocturnal temporal, parietal, and occipital lobe epilepsies (NTLE, NPLE, and NOLE respectively) are extremely rare and tend to overlap with SHE.² Generalised nocturnal epilepsies are likely to cause fewer diagnostic difficulties because there is greater recognition of the clinical characteristics of generalised seizures.⁴

Figure 1, above, provides an overview of normal sleep physiology, which helps contextualise nocturnal epilepsy and its differential diagnoses.⁴

What are the management approaches?

EPIDEMIOLOGY

More than 90% of the seizures in SHE occur during sleep. The term NFLE was replaced by SHE as these seizures occur during sleep regardless of the time of day, they are often extrafrontal originating in regions such as the temporal lobe (epileptogenic zone) and subsequently activate frontal lobe networks (symptomatic zone). Moreover, their motor activity is more excessive than in other types of frontal lobe epilepsy.^{2,6} SHE seizures occur during N2 of NREM sleep. As shown in figure 1, above, not only does N2 take up the majority of total sleep time, but it is also particularly prevalent within the first 30 minutes of sleep or shortly before »

Table 1

NREM parasomnia subtypes

Somnambulism (sleepwalking)	Behaviour ranging from sitting on the edge of the bed to walking around the bed, leaving the bedroom, dressing, cooking, escape attempts (e.g. trying to leave the house), and driving
Confusional arousal	Awaking from sleep with disorientation and slow to respond
Sleep terror	More abrupt arousal from sleep with expressions of intense fear and panic
Sexsomnia (sleep sex)	Engagement in sexual activities while asleep (including penetrative intercourse on rare occasions)
Sleep-related eating disorder	Getting up and consuming food while asleep, often quickly and excessively. This may include things that the patient would not normally eat, such as cigarettes. Injury can occur during careless food preparation

waking. SHE seizures follow these timelines, meaning that patients present with seizures throughout the night, but particularly within 30 minutes of going to sleep (even during daytime naps), and shortly before waking.⁴

Seizures in SHE are simple partial seizures, and therefore they involve no loss of consciousness. They may be preceded by an aura. As they occur at an N2 depth of sleep, they wake the patient up. Patients usually recall the seizures, describing auras of somatic sensations or feeling unable to breathe.⁴

The estimated prevalence of SHE is 1.8 per 100,000.⁷ The exact prevalence of SHE is difficult to determine because there are few epidemiological studies and the condition presents diagnostic difficulty.⁴ However, there is a consensus among specialists that SHE is probably not that rare, but often underestimated as a result of misdiagnosis.^{4,5}

Although the median age of onset is 14 years, SHE can occur at any age. It is often idiopathic, although there can be a positive family history in up to 40% of cases, and the genetic form shows an autosomal dominant inheritance pattern.⁴

CLINICAL HISTORY

When faced with a patient presenting with sleep-related motor and behavioural complaints, it is important to take a detailed history from the patient and also from a witness (normally a partner or family member). Assessment should address the following key questions:

1 Diagnosis: Is this epilepsy? If it is not epilepsy, are the movements and behaviour abnormal? As a general principle, epileptic seizures are brief, generally lasting no more than

2-3 minutes, and stereotyped. These principles hold true for nocturnal seizures. Certain seizures will be easier to recognise from sleep.

2 Safety: Does the patient pose a risk to self or others as a result of the sleep-related motor or behavioural complaint?

3 Triggers: Are there modifiable trigger factors? Is the presentation indicative of serious or treatable underlying pathology?

DIFFERENTIAL DIAGNOSES

Generalised epilepsies

Patients can have generalised tonic-clonic seizures (GTCS) while awake or asleep. In GTCS normally the muscles in the arms and legs become stiff, the patient becomes cyanosed, and there is rhythmic jerking and twitching. There may also be associated seizure markers including lateral biting of the tongue, incontinence, and myalgia. Juvenile myoclonic epilepsy is a genetic generalised epilepsy characterised by frequent myoclonic jerks in the morning, usually within the first hour of waking up, and GTCS. It generally begins in early adolescence^{3,5} and is a lifelong condition.⁸

Temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is common and patients may experience these seizures during both wakefulness and sleep. The characteristics of temporal lobe seizures are a rising epigastric feeling, déjà vu or jamais vu, olfactory hallucinations (e.g. metallic taste), auditory hallucinations, and automatisms (e.g. hand fidgeting, chewing, or lip smacking).² The presence of events while the patient is awake usually enables accurate clinical diagnosis of the sleep-related attacks in TLE.⁴

Sleep-related hypermotor epilepsy

The semiology of frontal lobe seizures in SHE is extremely variable between patients, although stereotyped for the individual. Common features are a rapid onset and offset, a short duration for each seizure (usually < 2 minutes), a high frequency of attacks throughout the night (3-8), and occurrence in clusters (e.g. several nights of seizures followed by weeks of remission). We have already described the aura and preserved consciousness.

Additionally, several semi-purposeful hyperkinetic movements may be seen, including bipedal or bimanual movements (running, cycling, or kicking), and axial movements (rocking, sitting or twisting). There can be prominent repetitive vocalisations that include unintelligible shouting or swearing. Tonic posturing is seen and includes head turning to the side of the seizure activity and fencing postures (contralateral shoulder abduction, external rotation, and elbow flexion). Additionally, patients tend to experience brief fragments of epileptic events that look like periods of arousal without dramatic motor features throughout NREM sleep.⁴ This is not an exhaustive list of the possible movements and behaviour seen in SHE. These events are often so bizarre and dramatic that they are frequently misdiagnosed as parasomnias or as non-epileptic attacks.

Parasomnias

In parasomnias complex motor or behavioural events occur during sleep in association with abnormal intrusions of one stage of sleep or wakefulness into another.⁶ They are divided into NREM parasomnias and REM parasomnias.

Table 1, opposite, summarises the NREM parasomnias, of which sleepwalking, confusional arousals, and sleep terrors are the most common. However, these conditions present as a spectrum and they often result in patients injuring themselves. They arise from a failure to make the transition between wakefulness and N3 of NREM sleep appropriately, meaning that certain parts of the brain are 'awake' while other parts are 'asleep'.⁴ This may help explain the profound complexity of the behaviours seen, and the patient's ability to interact strongly with the environment while retaining a near total lack of recall.

The association with N3 NREM sleep means that parasomnias tend to occur during the first third of sleep, normally around one to two hours after falling asleep. While they are very common in children, they occur in only 4% of adults.⁶

REM sleep behaviour disorder (RBD) is the most common REM parasomnia.⁶ Figure 1, p11, highlights atonia of the voluntary muscles during REM sleep, the stage in which vivid dreaming occurs. In the absence of that atonia, patients act out their dreams, normally in violent ways such as punching, kicking, or falling out of bed. Standing and walking is uncommon, but injury is not.

Patients recall the dreams if awoken by them, and the content is usually unpleasant. The events last seconds or minutes, usually in the final third of sleep. Age of onset for RBD is normally over 50 years and 80% of sufferers are men.

RBD is a strong prodromal marker for neurodegenerative disease, particularly the synucleinopathies (Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy). More than 80% of patients with RBD develop degenerative disease when followed up for more than 15 years.^{4,6}

Trying to differentiate between SHE and parasomnias can be very difficult.⁴ Table 2, below, summarises seven key questions that should help focus the

history to try to determine whether the presentation is SHE or a parasomnia.

The Frontal Lobe Epilepsy and Parasomnias (FLEP) Scale should also be used to help guide the history and differentiate between SHE and parasomnias. This is shown in table 3, p14.⁹ A score below zero favours parasomnias, 0-3 is inconclusive, and >3 favours SHE. The tool has positive and negative predictive values of 91-100% but should always be used in conjunction with a detailed clinical history.⁴

A complete history should aim to identify trigger factors and conditions that might be associated with SHE or parasomnias. Patients with SHE or parasomnias may complain of excessive daytime sleepiness resulting from interrupted sleep. Sleep deprivation is a trigger factor for seizures and parasomnias as is alcohol and/or drug abuse. It is important to enquire about recent febrile illness and stress, which can trigger parasomnias. There is a high prevalence of intellectual disabilities and psychiatric or behavioural problems in families with SHE.⁵

Nocturnal dissociative seizures

Dissociative seizures (pseudoseizures) can occur when patients are awake and during pseudosleep, where they appear asleep to the observer but the EEG demonstrates an awake pattern of electrical activity.

More than half (58%) of patients with non-epileptic attack disorder (NEAD) report some events during sleep in addition to those when awake. Isolated nocturnal dissociative seizures are rare.⁴ A history of events exclusively during sleep is more suggestive of epilepsy.¹⁰

Periodic limb movements of sleep

These movements involve recurrent, stereotyped, extension of the hallux and flexion of the ankle plus or minus the knee and hip. They last 0.5-5 seconds and occur at predictable intervals, every 5-90 seconds for a duration of minutes to hours. They are often a feature of restless legs syndrome.^{4,6}

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) presents with excessive daytime



Table 2

Differentiating sleep-related hypermotor epilepsy (SHE) from parasomnias

Key points in the history ⁴	SHE ^{2,4}	NREM parasomnias ^{2,4}	REM parasomnias (REM sleep behaviour disorder) ⁶
When do the events occur?	● Any time, but predominately within 30 minutes of sleep and soon before waking	● 1-2 hours after falling asleep, predominately in the first third of sleep	● Final third of sleep
How many events occur during one night?	● 3-8 events or more ● Clustering common	● 1-2 events ● Clustering uncommon	● 1-6 events ● Clustering uncommon
Does the patient remember anything about the event afterwards?	● Yes	● No	● Yes
What does the patient do during the event?	● Utters single noninteractive words or brief phrases ● Semi-purposeful stiffening and dystonic posturing, bipedal cycling, stays in bedroom ● Eyes open	● Complex interactive speech ● Complex, non-dystonic, interactive behaviours, can leave bedroom ● Eyes open	● Variable vocalisations with dream recall ● Noninteractive complex and violent oneiric behaviours, stays in bedroom ● Eyes closed
How long do the events last?	● 1-2 minutes ● Rapid onset, rapid offset	● 2-30 minutes ● Gradual onset, gradual offset, waxing and waning	● Seconds to 2 minutes ● Rapid onset, rapid offset
When did the events start?	● Any age, usually adolescence to 50 years	● First decade, peak age 5 to 10 years	● 50 years and older
Are the events always the same?*	● Highly stereotyped	● Not stereotyped	● Not stereotyped

*Witness descriptions can confound stereotypy either in favour of typically stereotyped events appearing or recalled as different, or typically non-stereotyped events appearing or recalled as the same

Table 3**The Frontal Lobe Epilepsy and Parasomnias (FLEP) Scale**

Clinical feature	Signalling question	Response	Score
Age at onset	At what age did the patient have their first clinical event?	< 55 years	0
		≥ 55 years	-1
Duration	What is the duration of a typical event?	< 2 minutes	+1
		2-10 minutes	0
		> 10 minutes	-2
Clustering	What is the typical number of events that occur in a single night?	1 or 2	0
		3-5	+1
		> 5	+2
Timing	At what time of night do the events most commonly occur?	Within 30 min of sleep onset	+1
		Other times (or if no clear pattern identified)	0
Symptoms	Are the events associated with a definite aura?	Yes	+2
		No	0
	Does the patient ever wander outside the bedroom during the events?	Yes	-2
		No (or uncertain)	0
	Does the patient perform complex, directed behaviours (e.g. picking up objects, dressing) during events?	Yes	-2
		No (or uncertain)	0
	Is there a clear history of prominent dystonic posturing, tonic limb extension, or cramping during events?	Yes	+1
		No (or uncertain)	0
Stereotypy	Are the events highly stereotyped or variable in nature?	Highly stereotyped	+1
		Some variability/uncertain	0
		Highly variable	-1
Recall	Does the patient recall the events?	Yes, lucid recall	+1
		No or vague recollection only	0
Vocalisation	Does the patient speak during the events and, if so, is there subsequent recollection of this speech?	No	0
		Yes, sounds only or single words	0
		Yes, coherent speech with incomplete or no recall	-2
		Yes, coherent speech with recall	+2
Total score =			

sleepiness as a result of disordered sleep due to prolonged and recurrent apnoeic events throughout sleep. It generally occurs in patients who are overweight. It can be a trigger factor for parasomnias, therefore it is important to enquire about night-time snoring and daytime sleepiness. OSA itself can also result in abnormal arousals that look similar to those from the fragmented epileptic events in SHE.⁴

Nocturnal panic attacks

Patients with panic disorders are at risk of nocturnal panic attacks. These present with awakening with intense fear. The patient is often unable to return to sleep for prolonged periods. There is retained awareness of events. Isolated nocturnal panic attacks are rare, so the presence of daytime panic disorder gives a clue to the diagnosis. There is also a close association with NEAD.⁴

Hypnic jerks (sleep starts)

These are a common part of normal sleep and consist of brief jerks of a limb or the whole body during the transition between wakefulness and sleep.

There can be a hallucinatory sensation of falling. Trigger factors include sleep deprivation, excessive caffeine, and stimulant intake.^{2,4}

INVESTIGATIONS

Most patients with sleep-related motor and behavioural complaints will have normal clinical examination findings. The examination should include looking for signs of injury, trigger factors (e.g. OSA), and underlying disease (such as focal neurology or Parkinsonism).

Many of the sleep-related motor and behavioural disorders are diagnoses that can be made on clinical grounds, and often investigation results will be normal. It is therefore important to rationalise the use of these investigations.

EEG

Half of patients with SHE have a normal EEG when awake and asleep.⁴ This is because seizures often originate in deeper parts of the brain not easily traced by surface EEG electrodes, and because epileptiform changes are often masked by the prominent movement and muscle artefact resulting from complex frontal seizure behaviours.

The EEG in parasomnia is also normal. Therefore, routine EEG does not normally advance the diagnosis of sleep-related motor and behavioural complaints. It is, however, worth ordering because in the 50% of cases where the trace does show epileptiform

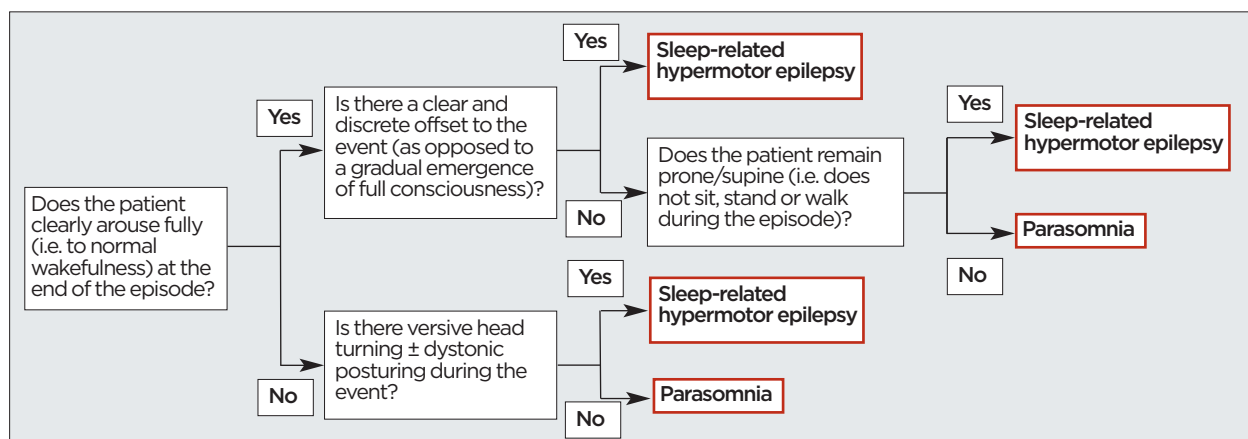


FIGURE 2
An algorithm to identify nocturnal events using video⁴

activity, further investigation is not required and the patient can commence treatment.

If a routine EEG is non-diagnostic, patients can undergo video telemetry. There is likely to be a long waiting list for this investigation as even large specialist centres in the UK normally only have a handful of telemetry beds and there are only around 30-40 telemetry units.¹¹

The investigation also involves an inpatient stay of one to two weeks, during which the EEG may still fail to detect epileptiform activity.⁴

Figure 2, above, shows a diagnostic algorithm that can be used as an aid in capturing SHE or parasomnias using video observation. This is accurate in 94% of cases.⁴

MRI

An MRI should be ordered because there is a small chance (14%) that it may identify a treatable local epileptogenic abnormality in SHE. However, the majority of MRI scan results in SHE and parasomnias will be normal.⁴

Polysomnography

Polysomnography is the gold standard investigation, but it is not easily accessible in the UK. There are fewer than 90 centres offering the investigation, and long waiting times.¹²

It combines EEG with various other investigations including eye movement, respiratory airflow, electromyography, and video.² It is particularly helpful when trying to identify the co-occurrence of trigger factors such as OSA. The EEG may still fail to identify epileptiform discharges, for the reasons mentioned earlier.

Home video

Patients and partners should be encouraged to try and record events at home if possible, e.g. using a smart phone.

MANAGEMENT

Nocturnal epilepsy syndromes tend to respond well to antiepileptic drug therapy and the avoidance of seizure triggers. All patients should receive counselling about seizure precautions, complications, and driving safety.

Drugs

There is a paucity of evidence on specific treatments for nocturnal epilepsies. As a general principle, they are treated using the same range of drugs as focal and generalised awake seizures.¹³ Lamotrigine and carbamazepine are usually good options for focal epilepsy.

Lamotrigine tends to be better tolerated, although patients should be warned that they should stop the drug immediately if they develop a rash. This tends to occur less frequently if dosing is gradually increased. Lamotrigine is normally started at a dose of 25 mg once daily for 14 days, increased to 50 mg once daily for a further 14 days, then increased in steps of up to 100 mg every 7-14 days. The usual maintenance dose is 100-200 mg daily, in 1-2 divided doses.¹⁴

Levetiracetam also works well for focal epilepsies, although there is some evidence that its efficacy is less than that of lamotrigine (when both are compared with carbamazepine).¹⁵ However, there is a lack of head-to-head trials.

Other options include oxcarbazepine and topiramate.¹³ There is emerging evidence that lacosamide may be effective in nocturnal focal epilepsy, with up to 65% of patients with drug-resistant seizures achieving ≥ 50% reduction in seizure frequency.¹⁶

Chronopharmacology describes the use of differential drug dosing times to reduce seizures at peak times, while keeping the total daily dose the same.

For nocturnal seizures, this involves increasing the evening dose and reducing the morning dose. It may provide some benefit, although the evidence is limited.¹³

Clonazepam is a broad spectrum benzodiazepine that may work well for parasomnias and the other non-epileptic disorders of movement and behaviour. The typical dose is 0.5-1 mg at night.²

Surgery

The use of epilepsy surgery in SHE is rare, as surgery is reserved for drug-resistant cases with lesional aetiology. A recent study demonstrated that in 80% of patients with lesional nocturnal epilepsy, 76% of patients achieved freedom from seizures.¹⁷

Trigger management

Several studies have shown that managing OSA with continuous positive airway pressure helps reduce seizures and parasomnias. Insomnias can be managed with melatonin, although the effect of melatonin on seizure frequency is unclear.¹³

SAFETY

Patients and families should be advised to take seizure precautions including moving the mattress onto the floor, removing obstructing furniture, timing seizures and learning to use buccal midazolam or call 999 after 3-5 minutes during a seizure, and training in first aid and cardiopulmonary resuscitation.¹³

A patient must not drive and must notify the DVLA following a seizure during sleep. Relicensing may be granted if, over the course of at least one year from the date of the sleep seizure, the patient establishes a history or pattern of seizures occurring only ever while asleep. Alternatively, regardless of »

key points

SELECTED BY

Dr Phillip Bland

Former GP, Dalton-in-Furness, UK

Epilepsy usually presents with seizures occurring during both wakefulness and sleep. However, there are some epilepsies in which seizures appear mainly or exclusively during sleep. Nocturnal epilepsies account for 10-15% of all epilepsies, and 80% of nocturnal epilepsies in adults are focal. They present a diagnostic challenge as they can be difficult to differentiate from normal movements and behaviour during sleep and also from several non-epileptic, sleep-related, motor and behavioural disorders. Sleep-related hypermotor epilepsy (SHE) is often idiopathic, although there can be a positive family history in up to 40% of cases, and the genetic form shows an autosomal dominant inheritance pattern. Although the median age of onset is 14 years, this type of epilepsy can occur at any age.

More than 90% of the seizures in SHE occur during sleep. Seizures occur during the N2 stage of NREM sleep so are particularly likely to occur within 30 minutes of falling asleep (even during daytime naps), and shortly before waking. Seizures in SHE are simple partial seizures which easily wake the patient so that they will usually be able to recall the seizures, often describing auras of somatic sensations or feeling unable to breathe.

SHE seizures have a rapid onset and offset, a short duration (usually < 2 min), and a stereotyped motor pattern for that individual. Several semi-purposeful hyperkinetic movements may be seen, including bipedal or bimanual movements (running, cycling, or kicking), and axial movements (rocking, sitting or twisting). There can be prominent repetitive vocalisations that include unintelligible shouting or swearing. Tonic posturing may occur and includes head turning to the side of the seizure activity and fencing postures. Additionally, patients tend to experience brief fragments of epileptic events that look like periods of arousal without dramatic motor features throughout NREM sleep.

In parasomnias complex motor or behavioural events occur during sleep in association with abnormal intrusions of one stage of sleep or wakefulness into another. Sleepwalking, confusional arousals, and sleep terrors are the most common NREM parasomnias. The most common REM parasomnia is REM sleep behaviour disorder, in which patients act out their dreams, normally in violent ways such as punching, kicking, or falling out of bed. It can be very difficult to differentiate between SHE and parasomnias but this can be facilitated by asking seven key questions including 'When do the events occur?' and 'How many events occur during one night?' SHE is characterised by a high frequency of attacks (3-8 events or more per night), and occurrence in clusters.

Many of the sleep-related motor and behavioural disorders are diagnoses that can be made on clinical grounds, and often investigation results will be normal. Half of patients with SHE have a normal EEG both when awake and asleep, and as few as 14% of patients will have an abnormal MRI scan.

preceding seizure history, if a person establishes a pattern of asleep seizures only (all seizures had onset during sleep), starting at least three years prior to licence application and there have been no other unprovoked seizures during those three years, a licence may be issued.¹⁸

COMPLICATIONS

As a whole, epilepsy remains a major concern for premature death.^{19,20} Individuals with epilepsy are 20-40 times more likely to die a sudden death than those without epilepsy.¹³ This risk of sudden unexpected death in epilepsy (SUDEP) remains the same for SHE as for other epilepsies.²¹ One might have expected SUDEP risk to be even higher in SHE than the other epilepsies given the daily occurrence of seizures during sleep in this condition and the fact that nocturnal seizures independently increase the risk of SUDEP. However, GTCS also independently increase the risk of SUDEP, and SHE is associated with a low occurrence of these seizures.²² Other SUDEP risk factors include sleeping in the prone position, and a chronic history of epilepsy. Factors that can reduce risk of SUDEP include adequate seizure control, nocturnal supervision (e.g. sharing a bedroom), and epilepsy alarms.¹³

CONCLUSION

The diagnosis of nocturnal epilepsy, parasomnias and other non-epileptic abnormal movement and behaviour disorders in sleep largely remains clinical and a careful history is the most important diagnostic step. Observation of events by video may also be helpful.

Drug management of the nocturnal epilepsies is similar to that for awake epilepsy, and there should also be a focus on dealing with trigger factors such as OSA and other triggers of poor sleep. Nocturnal epilepsy can be a risk factor for SUDEP.

Competing interests: None

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Useful information

For healthcare professionals
SIGN 143. Diagnosis and management of epilepsy in adults
www.sign.ac.uk/assets/sign143_2018.pdf

UpToDate
www.uptodate.com/contents/sleep-related-epilepsy-syndromes#H787554864

For patients
Epilepsy Action
www.epilepsy.org.uk/info/wellbeing/sleep

National Sleep Foundation
www.sleepfoundation.org/sleep-disorders-problems/disease-and-sleep/epilepsy

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Tackling medication overuse headache in primary care

Duncan C, Watson D. Tackling medication overuse headache in primary care.

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Dr Callum Duncan
BSc MBChB PhD FRCP
Consultant Neurologist, Aberdeen Royal Infirmary,
Aberdeen, UK

Dr David Watson
MBChB FRCGP FRCP DRCOG AFOM
GPwSI Headache,
Aberdeen, UK



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AUTHORS

Dr Callum Duncan
BSc MBChB PhD FRCP
Consultant Neurologist,
Aberdeen Royal
Infirmary, Aberdeen, UK

Dr David Watson

MBChB FRCGP FRCP
DRCOG AFOM
GPwSI Headache,
Aberdeen, UK

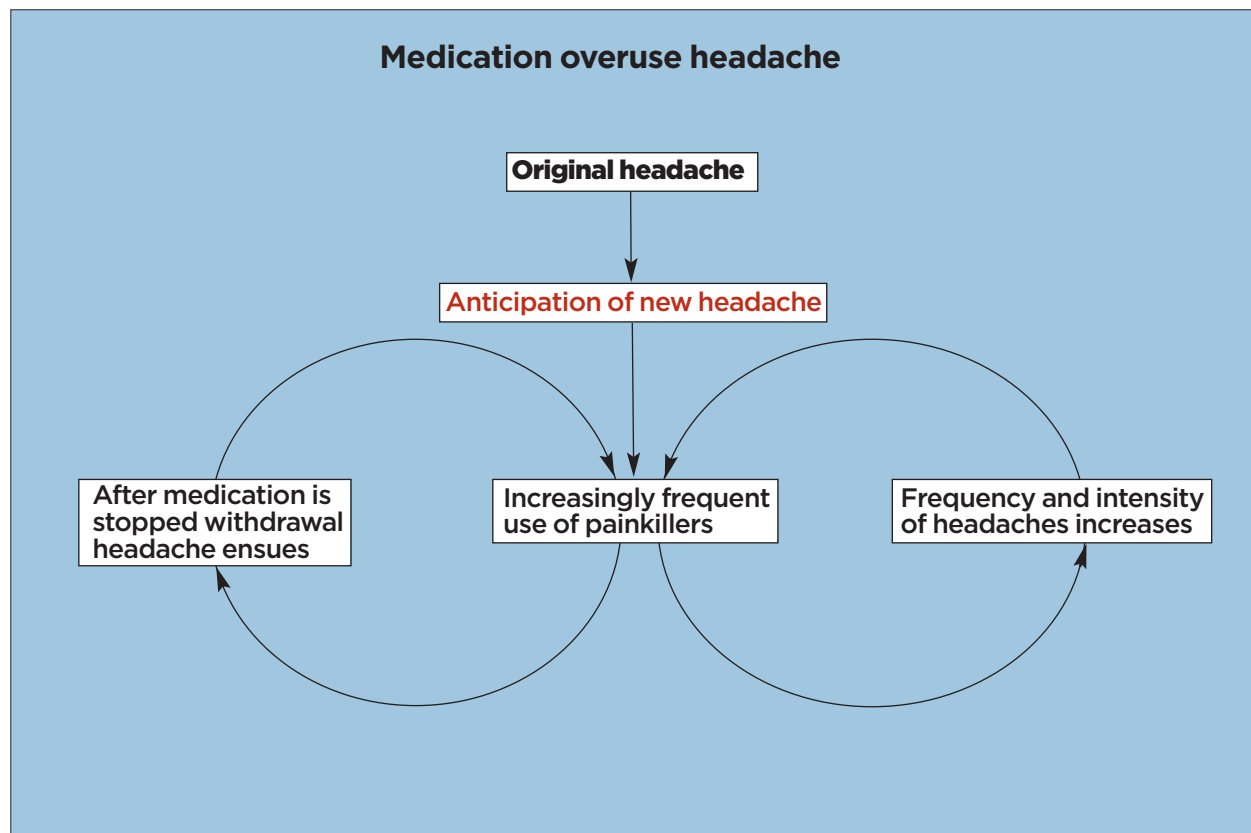


FIGURE 1

The vicious cycle of medication overuse headache

What are the main risk factors?

How should diagnosis be confirmed?

What are the management approaches?



MEDICATION OVERUSE HEADACHE (MOH) IS VERY COMMON AFFECTING 1-2% OF THE POPULATION

worldwide.¹ It occurs as a complication of the management of primary headache disorders, mainly migraine and tension type headache (TTH).

In the majority of patients this is a complication of migraine² and patients with MOH often have a chronic migraine pattern which develops from episodic migraine. MOH does not occur in cluster headache unless there is associated migraine.³ In these cases the patient experiences a superimposed migraine headache that worsens but when the causative medication is withdrawn the migraine headache improves leaving the underlying cluster headache.

Frequent use of any medication used

for the acute treatment of headache can result in MOH.^{1,2} There is often anticipatory anxiety (taking acute medication because of concern that a headache may start) and the frequency and intensity of headaches increases with increasing medication use. The underlying headache pathways become sensitised and the treatment becomes the cause rather than the cure. A vicious cycle of

‘The underlying headache pathways become sensitised and the treatment becomes the cause rather than the cure’

increased medication use and increasing headache ensues, see figure 1 above. MOH can also arise when acute medication is used for another painful condition such as rheumatoid arthritis.⁴ This only occurs in patients where there is a preceding primary headache disorder, usually migraine.

MOH is defined as headache on 15 or more days per month that has evolved along with the frequent use of acute medication, for more than three months,⁵ (see box 1, p18). It normally demonstrates a chronic migraine pattern (15 or more headache days per month of which 8 or more fulfil the criteria for migraine). Importantly, not all patients with chronic migraine who also use acute treatment frequently suffer from MOH; some just have poorly controlled migraine.²

Box 1

Medication overuse headache diagnostic criteria⁵

Description

Headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more, or 15 or more days per month, depending on the medication) for > 3 months. It usually, but not invariably, resolves after the overuse is stopped

Diagnostic criteria

- Headache occurring on 15 or more days per month in a patient with a preexisting headache disorder
- Regular overuse for > 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache:
 - Triptans, ergots, opioids, combination analgesics or multiple drug classes. Regular intake on 10 or more days per month for >3 months
 - Simple analgesics (e.g. aspirin, ibuprofen and paracetamol). Regular intake on 15 or more days per month for >3 months
- Headache not better accounted for by another ICHD-3 diagnosis

CAUSATIVE AGENTS

Any medication used for the acute treatment of headache can cause MOH.^{1,2} For triptans, combination analgesics and opioids 10 or more days use per month is considered sufficient to cause MOH, and for simple analgesics (aspirin, ibuprofen and paracetamol) 15 days per month.⁵

When prescribing acute treatment, patients should be counselled about the risk of MOH. Patients using frequent combination analgesics and opioids are particularly at risk of MOH and these should be avoided.⁶

A good rule of thumb is to limit acute treatment to 2 days per week in patients with migraine and TTH.⁶ This rule does not apply to patients with cluster headache where the safe limit of triptan use is 2 doses per day for injectable sumatriptan and 3 doses per day for nasal zolmitriptan.⁷

RISK FACTORS

MOH occurs in patients with a preexisting tendency to a primary headache disorder, mainly migraine and TTH.

The main risk factors for the development of MOH are frequent use of acute medication and frequent headache (see table 1, above). The more frequent the headache the more likely it is that the patient will tip over into MOH. Other risk factors include: low socioeconomic status, smoking, high BMI, anxiety or depression, another painful condition and a family history of MOH or substance misuse.¹

DIAGNOSIS

MOH should be suspected in any patient frequently using acute medication for

headache, including over the counter (OTC) products. It should also be considered in patients with chronic daily headache especially chronic migraine and chronic TTH. Around a third of patients with chronic daily headache (> 15 days/month) have MOH.¹

An appropriate neurological examination should include fundoscopy to exclude papilloedema, visual fields, cranial nerves, power and reflexes in the limbs and the Romberg test for balance. Blood pressure (BP) should also be checked. If the BP is very high this can cause headache. If it is low certain medications used to prevent migraine such as beta-blockers and candesartan may lower it further causing postural hypotension.

‘Any medication used for the acute treatment of headache can cause medication overuse headache’

As mentioned above, MOH is only an issue in cluster headache when the patient also suffers from migraine.³ Patients with cluster headache should be offered an adequate supply of triptans. This should be calculated according to their history of cluster bouts, and based on the manufacturer’s recommended maximum daily dose.⁷

The diagnosis of MOH is based on a thorough history which can be aided by the use of headache diaries.

Table 1

Risk factors for medication overuse headache

- Underlying primary headache disorder
- Frequent headache
- Frequent acute medication use
- Another painful condition
- Anxiety or depression
- Low socioeconomic status
- High BMI
- Smoking

Table 2

Diagnosis of medication overuse headache

- Establish how many days the patient suffers from mild, moderate or severe headache
- Ask specifically about completely clear days
- Establish how many days acute medication is used
- Ask specifically about over the counter medication and where medication is kept
- Establish if there has been an escalation in headache frequency over time

Typically, chronic migraine has developed gradually from episodic migraine with increasing acute medication use. Patients often underestimate the number of headache days concentrating on significant headache days and an important question to ask is how many completely clear days there are. What initially sounds like episodic migraine may turn out to be chronic migraine.

It is important to ascertain how much acute medication is used and to enquire specifically about OTC medication as patients may only volunteer details about prescribed medication. Another useful question to ask is where acute medication is kept. The more locations (home, work, bag) the more likely that there is medication overuse.

The number of days per month that acute medication is used is more important than the total amount of medication taken, for example paracetamol used once daily is sufficient to cause MOH, whereas paracetamol used 4 times per day 10 days per month is not, see table 2, above.

Waking up with a headache is a feature that often raises concern about

key points

SELECTED BY

Dr Phillip Bland

Former GP, Dalton-in-Furness, UK

Medication overuse headache (MOH) affects 1-2% of the population worldwide. It occurs as a complication of the management of primary headache disorders, primarily migraine and tension type headache (TTH). MOH does not occur in cluster headache unless there is associated migraine.

MOH is defined as headache occurring on 15 or more days per month, that has evolved in association with the frequent use of acute medication over a period of more than 3 months. Normally, it has a chronic migraine pattern i.e. 15 or more headache days per month of which 8 or more fulfil the criteria for migraine. Importantly, not all patients with chronic migraine who frequently use acute treatment have MOH; some have poorly controlled migraine.

Any medication used for the acute treatment of headache can cause MOH. In the case of triptans, combination analgesics and opioids, use on 10 or more days per month is considered sufficient to cause MOH, whereas for simple analgesics (aspirin, ibuprofen and paracetamol) the threshold is 15 days per month. A good rule of thumb is to limit acute treatment to 2 days per week in patients with migraine and TTH. This rule does not apply to patients with cluster headache where the safe limit of triptan use is 2 doses per day for injectable sumatriptan and 3 doses per day for nasal zolmitriptan.

The diagnosis of MOH is based on a thorough history which can be aided by the use of headache diaries. Typically, episodic migraine has gradually become chronic migraine in association with increasing acute medication use. Patients often underestimate the number of headache days by concentrating on significant headache days and it is important to ask how many completely clear days there are. It is important to enquire about over the counter medication and where the patient keeps their medication. Medication kept in multiple locations may be an indicator of overuse. The number of days per month on which acute medication is used is more important than the total amount of medication taken.

The three treatment options for MOH are: abrupt withdrawal alone, abrupt withdrawal with prophylaxis, or prophylaxis without withdrawal. Opioids should be withdrawn gradually. Abrupt withdrawal is often associated with transient worsening of headache frequency and intensity and patients should be warned to expect this. Referral to a neurology or specialist headache clinic should be considered if: appropriate management of MOH has not been successful, advice is required about management of the underlying primary headache disorder, or there is concern that there may be an underlying sinister cause.

a possible underlying sinister cause for headache. However, this is a common feature of MOH. It is important to consider whether headache on awakening could be due to withdrawal of medication overnight and if the headache improves when the overused medication is taken.

'The number of days per month that acute medication is used is more important than the total amount of medication taken'

Withdrawal of the overused medication results in improvement in headache frequency in a significant proportion of patients. The International Classification of Headache Disorders previously required improvement in headache frequency following successful withdrawal of the overused medication before the diagnosis could be confirmed. It is now recognised that not all patients improve following medication withdrawal and this criterion has been removed in the latest version.⁵

MANAGEMENT

It is important to remember that MOH is a risk in any patient using acute treatment for primary headache disorders, particularly migraine and TTH. When prescribing acute therapy, patients should be advised to limit acute treatment to a maximum of 2 days per week,⁶ see table 3, above right. Combination analgesics and opioids should be avoided.^{6,7}

Once MOH is established the best management strategy is not clear. The available evidence comes from a range of small randomised, controlled trials, non-comparative observational, and retrospective studies.⁶ Three strategies are recommended:

- Abrupt withdrawal alone either by simple advice or by a structured detoxification programme. Prophylaxis may then be considered after a delay
- Abrupt withdrawal with prophylaxis started immediately
- Initiating prophylaxis without withdrawal
- Opioids should be withdrawn gradually

There are no adequately sized studies

Table 3

How to manage medication overuse headache

- Warn patients about the risks of medication overuse headache (MOH) before starting acute treatment
- Limit acute treatment to 2 days per week to prevent MOH
- Avoid opioids where possible as acute treatments
- Most patients with MOH can be managed as outpatients
- A no blame approach should be used
- The management strategy should be individualised
- Abrupt withdrawal alone, abrupt withdrawal and immediate introduction of a preventative, introduction of a preventative without withdrawal are all effective strategies
- Opioids should be withdrawn gradually
- Patients should be warned to expect transient worsening of headache frequency and intensity associated with medication withdrawal

that compare strategies. In those studies looking at abrupt withdrawal alone, the length of withdrawal period before starting preventative medication has not been clearly defined.⁶

'Abrupt withdrawal of the overused medication is often associated with transient worsening of headache frequency and intensity'

Abruptly withdrawing the overused medication is often associated with transient worsening of headache frequency and intensity and patients should be warned to expect this. Other more typical withdrawal symptoms may also occur with opioids or combination analgesics with a high opioid content, but are much less likely with triptans and NSAIDs.¹ Withdrawal headache is shortest for triptans and longest for combination analgesics and opioids. It is in the order of weeks. Patients should generally be reassessed after 2 months.

In the majority of cases, medication withdrawal can be successfully

»

managed as an outpatient, particularly in patients with uncomplicated MOH.⁸ There is no evidence to support using prednisolone to aid medication withdrawal.⁹ Support from a headache specialist nurse can significantly improve success rates.¹⁰ For patients with complicated MOH, inpatient withdrawal may be more effective than advice alone or a structured outpatient withdrawal programme.¹¹ Access to inpatient withdrawal is, however, limited in the UK and this is rarely a realistic option outside the larger headache centres.

Following successful withdrawal, previously ineffective preventative treatments may be effective when reintroduced.¹² Around 20-40% of patients relapse in the first year, after that relapse is uncommon.¹ There is, however, considerable debate as to whether withdrawal is necessary and there are likely to be two groups of patients: those with poorly managed frequent migraine and those who have MOH. Small RCTs have reported a reduction in headache days using topiramate or valproate.⁶ There are no studies on other oral migraine preventatives.

The use of botulinum toxin as a preventative therapy in chronic migraine was investigated in the PREEMPT studies.^{13,14} The protocol did not mandate medication withdrawal and post hoc analysis showed no difference in the effectiveness of botulinum toxin A in patients who were and those who were not overusing acute medication.¹⁵ Both NICE¹⁶ and the Scottish Medicines Consortium¹⁷ mandate that medication overuse must be addressed before considering botulinum toxin A, but once addressed botulinum toxin A is equally effective in those with and without successful withdrawal.^{15,18}

The same is likely to be true for the new CGRP monoclonal antibodies of which erenumab was granted a European licence in July though this has not yet been through the approval process for NHS use in the UK.

REFERRAL

It is important to explain to patients that MOH is common and that addressing medication overuse can have a meaningful impact on headache frequency in most cases.

A no fault approach should be adopted and patients encouraged to seek support from family, friends and work colleagues especially in the first two weeks when the headache may get worse.

The majority of patients with MOH

can be successfully managed in primary care. The underlying pattern is usually chronic migraine and once medication overuse is addressed this can usually be managed successfully. Patients should be aware that headache does not always improve with medication withdrawal and that appropriately managing the underlying primary headache disorder can be effective and that MOH often hampers the effectiveness of the standard preventative treatments.

Referral to a neurology or specialist headache clinic should be considered if:

- Appropriate management of MOH has not been successful
- Advice is required about management of the underlying primary headache disorder
- There is concern that there may be an underlying sinister cause

In cases where there is concern about the possibility of an underlying sinister cause, open access imaging may help management. However, all patients who are referred for imaging should be informed that scanning may show incidental abnormalities.¹⁹ Studies have shown that any reassurance a patient gets from a normal scan tends to fade by 12 months if the headache is still present.²⁰

Competing interests: None

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Useful information

The Migraine Trust
www.migrainetrust.org

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GPs play a vital role in identifying and managing juvenile idiopathic arthritis

Renton WD, Ramanan AV.

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Dr William D Renton
MBBS FRACP
Clinical Fellow in Paediatric Rheumatology

Bristol Royal Hospital
for Children, University Hospitals Bristol
NHS Foundation Trust, Bristol, UK

Professor Athimalaipet V Ramanan
FRCPCH FRCP
Consultant Paediatric Rheumatologist

Bristol Royal Hospital for Children,
University Hospitals Bristol NHS Foundation Trust
and Bristol Medical School,
University of Bristol, Bristol, UK



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GPs play a vital role in identifying and managing juvenile idiopathic arthritis

AUTHORS Dr William D Renton

MBBS FRACP
Clinical Fellow in
Paediatric
Rheumatology

Bristol Royal Hospital
for Children, University
Hospitals Bristol
NHS Foundation Trust,
Bristol, UK

Professor Athimalaipet V Ramanan

FRCPCH FRCP
Consultant Paediatric
Rheumatologist

Bristol Royal Hospital for
Children, University
Hospitals Bristol NHS
Foundation Trust and
Bristol Medical School,
University of Bristol,
Bristol, UK

FIGURE 1

Right ankle swelling
in a seven-year-old
girl with oligoarticular
juvenile idiopathic
arthritis



JUVENILE IDIOPATHIC ARTHRITIS (JIA), FORMERLY REFERRED TO AS JUVENILE CHRONIC

arthritis or juvenile rheumatoid arthritis, is the most common rheumatic disease of childhood. It affects approximately 1-4 per 1,000 children under the age of 16.¹ Girls are more commonly affected than boys in an overall ratio of approximately 3:2 but the ratio varies significantly between JIA subtypes. It is a heterogeneous condition ranging from insidious arthritis affecting only one to two joints to florid and life-threatening systemic onset arthritis (previously called Still's disease).

While the exact aetiology is not entirely understood, the disease is likely to be caused by a combination of genetic and environmental factors.² Around 10-20% of patients have associated uveitis and this is a major cause of long-term morbidity.³ Prompt diagnosis and initiation of treatment is important to minimise permanent complications of chronic

arthritis. Coordinated, multidisciplinary care is required to achieve optimal outcomes.

GPs play a vital role in the identification and ongoing care of children and adolescents with JIA.

DIAGNOSIS

Classification criteria

The International League of Associations for Rheumatology (ILAR) classification is the most widely used and accepted classification system for JIA.⁴ Arthritis is defined as swelling within a joint, or limitation in the range of motion with joint pain or tenderness. JIA is arthritis of at least six weeks' duration with onset of disease before the age of 16, observed by a physician, that is not the result of a primarily mechanical disorder or any other identifiable cause.

JIA is a clinical diagnosis and unlike adults with arthritis, radiological and laboratory investigations are less likely to be of help. The categories of JIA are based on clinical and laboratory characteristics (see table 1, p22).

How do children with JIA present in primary care?

What are the treatment options?

How should patients be reviewed and followed up?

Clinical features

JIA is a heterogeneous condition even within JIA categories. Arthritis is typically characterised by early morning stiffness that eases as the day goes on. Swelling, pain, restricted range of movement and muscle wasting are also frequently seen.

Children with oligoarticular disease typically present with gradual onset arthritis of the large joints, see figure 1, above. This form of arthritis predominantly affects preschool children. They are generally otherwise very well and remain active despite their arthritis. Signs such as swelling, a limp, developmental delay or reluctance to use an affected limb may be observed.

Patients with polyarticular JIA may have more systemic symptoms such as lethargy, malaise and even low-grade fever. Rheumatoid factor (RF) positive polyarthritis resembles adult rheumatoid arthritis and tends to affect multiple large and small joints symmetrically (especially the proximal interphalangeal and metacarpophalangeal joints).

SPECIAL REPORT

JUVENILE IDIOPATHIC ARTHRITIS

RF negative polyarticular JIA is usually less symmetrical.

Enthesitis (tenderness at the insertion of a tendon, ligament, joint capsule or fascia to bone) and axial arthritis (including sacroiliac joints) are common in children with psoriatic and enthesitis-related JIA.

Systemic onset JIA is genetically and physiologically distinct from other JIA subtypes.^{5,6} Prolonged fever is a hallmark of the disease and classically follows a quotidian pattern (fever rising to > 39°C once a day and returning to < 37°C between peaks). The fevers are almost always accompanied by a characteristic rash that commonly affects the trunk and proximal extremities. The rash is usually characterised by discrete erythematous macules that disappear within hours of appearing. Arthritis may be a relatively late clinical finding.

Evidence of immune activation, including lymphadenopathy and hepatosplenomegaly, is often seen. Macrophage activation syndrome (MAS) is a severe and life-threatening complication that can affect a small percentage of patients with systemic onset JIA.⁷ MAS is an uncontrolled and dysfunctional immune response characterised by persistent fever, pancytopenia, coagulopathy and hyperferritinaemia.⁸ Any suspicion of this condition, which is a medical emergency with significant mortality rates, should prompt immediate hospital referral for further assessment.

The paediatric Gait, Arms, Legs, Spine (pGALS) examination is a helpful framework for examining children and adolescents with possible or established arthritis.⁹ Joints including the cervical spine, temporomandibular joints, hips and

subtalar joints must not be overlooked.

Uveitis affects as many as 20% of patients with JIA and is usually asymptomatic in the early stages. In some cases, it can precede the onset of arthritis. It is sight threatening if not detected and treated. Some clinical signs including cataracts, keratic precipitates and irregular pupils secondary to synechiae can be observed by direct ophthalmoscopy (see figure 2, opposite).

Differential diagnoses

Musculoskeletal complaints are one of the most common reasons that children and adolescents seek medical attention. There is a vast range of causes that range from benign to life threatening. Non-inflammatory causes of joint pain, including growing pains, are much more common than inflammatory rheumatic

Table 1

International League of Associations for Rheumatology (ILAR) Classification of JIA⁴

Arthritis type		Definition
Systemic onset		Arthritis in 1 or more joints with, or preceded by, fever of at least 2 weeks' duration that is documented as daily for at least 3 days and accompanied by one or more of the following: ● Evanescent (non-fixed) erythematous rash ● Generalised lymph node enlargement ● Hepatomegaly and/or splenomegaly ● Serositis
Oligoarticular	Persistent	Arthritis affecting 1-4 joints during the first 6 months of the disease and affecting not more than 4 joints throughout the disease course
	Extended	Arthritis affecting 1-4 joints during the first 6 months of the disease and affecting a total of more than 4 joints after the first 6 months of disease
Polyarticular	RF negative	Arthritis affecting 5 or more joints during the first 6 months of the disease; a test for RF is negative
	RF positive	Arthritis affecting 5 or more joints during the first 6 months of the disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive
Psoriatic		Arthritis and psoriasis, or arthritis with at least 2 of the following: ● Dactylitis ● Nail pitting or onycholysis ● Psoriasis in a first-degree relative
Enthesitis related		Arthritis and enthesitis, or arthritis with at least 2 of the following: ● The presence, or a history, of sacroiliac joint tenderness and/or inflammatory lumbosacral back pain ● The presence of HLA-B27 antigen ● Onset of arthritis in a male over 6 years of age ● Acute (symptomatic) anterior uveitis ● History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative
Undifferentiated		Arthritis that fulfils criteria in no category or in 2 or more of the above categories

diseases and usually have distinct characteristics, see table 2, below.^{10,11} Taking a careful history and systematic examination in all children with possible JIA is important to rule out other differential diagnoses, see table 3, p24.¹²⁻¹⁵

Investigations

There is no single test that accurately diagnoses JIA. Tests to increase diagnostic certainty and exclude mimics are required in some cases. A reasonable set of first-line blood tests for suspected JIA includes: a full blood count (and blood film), urea, creatinine, electrolytes, liver function tests, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Normal blood test results do not preclude a diagnosis of JIA and should not delay referral for a specialist opinion if clinical suspicion remains high.

A full blood count may show signs consistent with inflammation such as anaemia, leucocytosis and thrombocytosis, but may also be within normal limits. ESR and CRP are usually elevated but may also be normal, particularly in children with oligoarthritis.

Investigations such as antinuclear antibodies (ANA), rheumatoid factor (RF), cyclic citrullinated peptide (CCP) antibodies and human leukocyte antigen B27 (HLA-B27) do not play a significant role in the diagnosis of JIA. ANA can be found in up to 5-18% of healthy children; usually at low titres (up to 1:320), however higher titres may occur.¹⁶⁻¹⁹ RF and CCP antibodies are only positive in a small minority of children and adolescents with JIA and can also be seen in healthy individuals, often as a

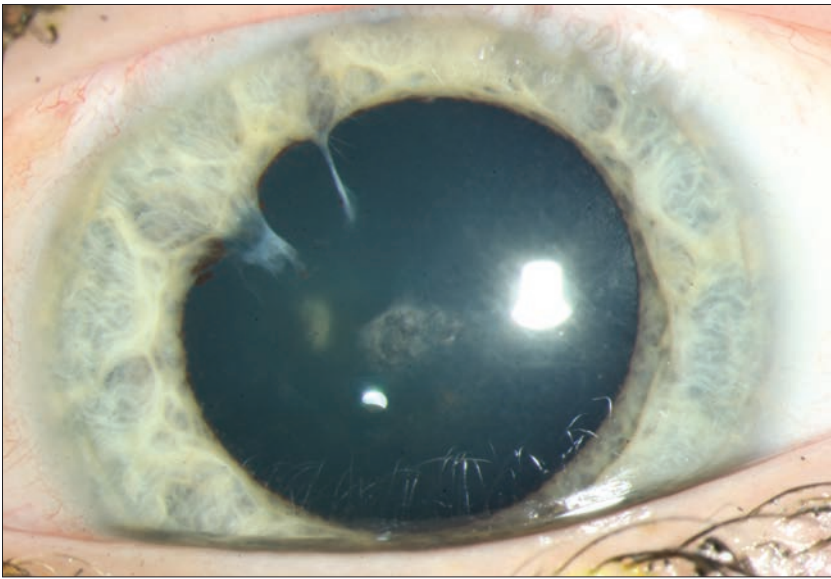


FIGURE 2
Central cataract and irregular pupil due to posterior synechiae in a 15-year-old girl with juvenile idiopathic arthritis related anterior uveitis

response to recent infection. HLA-B27 is associated with enthesitis-related arthritis but is also present in around 10% of the general population.²⁰

Plain X-rays may show acute changes such as a joint effusion but are unlikely to show more specific changes such as joint erosions except in very advanced disease. However, they are useful for excluding differentials such as trauma, malignancy and infection.

Other imaging modalities including ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) can all play an important role in the diagnosis and ongoing management of JIA. Each investigation has its benefits and drawbacks and specialist input may

be required to determine the best approach for an individual patient.²¹

MANAGEMENT

The goals of treating patients with JIA are to: control signs and symptoms; prevent structural damage; avoid comorbid conditions and drug toxicities; and optimise function, growth and development, quality of life, and social participation by abrogation of inflammation. Clinical remission should be the primary target for all patients and treatment should be adjusted until this is achieved.²²

The healthcare team should involve the patient and parents in therapeutic decisions. Increasingly early aggressive treatment is given as early initiation of therapy increases the likelihood of a response to first-line treatments and of achieving drug-free remission later in life.²³⁻²⁵

Referral and ongoing review

All patients with suspected JIA should be urgently referred to a specialist paediatric rheumatology team that may consist of a paediatric rheumatologist, general paediatrician with an interest in paediatric rheumatology or adult rheumatologist with an interest in paediatric rheumatology (operating within a formal paediatric rheumatology clinical network).

Patients with confirmed JIA need access to a team including their GP, paediatric rheumatology nurse specialists, ophthalmologists, paediatric physiotherapists, paediatric clinical psychologists, paediatric occupational therapists, podiatrists and health visitors or school nurses. Patients with active

Table 2

Differentiating limb pains in children

Growing pains	Concerning causes of limb pains
Well child	Fever, weight loss, pallor
Non-articular and poorly localised (shins, calves, thighs, popliteal fossae)	Articular
Bilateral	Can be unilateral or bilateral
Intermittent with pain-free intervals	Persistent
Normal gait	Limp or refusal to walk
Occur late in the day or at night	Can occur at any time
Normal clinical examination	Objective signs of inflammation (swelling, reduced range of motion, erythema, focal tenderness)

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disease should be seen as required and at intervals of no longer than four months.²⁶

Non-pharmacological interventions

Children with JIA are at risk of low bone mineral density (independent of steroid use) and pathologic fractures are not uncommon.²⁷ A balanced diet including adequate calcium and vitamin D intake is recommended. Regular exercise leads to better outcomes and should be encouraged in all patients.^{28,29} Simple strategies including heat packs and warm baths can help alleviate joint pains and stiffness. Appropriate footwear as well as splints and orthotics are indicated in some cases.³⁰ Other supportive therapies including physiotherapy, occupational therapy and psychology are vital to the effective management of patients with JIA.

Simple analgesics and NSAIDs

Paracetamol has a role in managing symptoms of JIA although evidence for its efficacy is limited. NSAIDs are the first-line medication for the treatment of

inflammation in children with JIA. They are useful analgesics and while they have some anti-inflammatory properties, they are unlikely to lead to clinical remission in isolation.³¹ They are generally very well tolerated in children although possible side effects include gastrointestinal upset, rash and mood changes. Many children with asthma can take NSAIDs safely however caution is advised as they can worsen symptoms.

Ibuprofen, naproxen, diclofenac, indomethacin, meloxicam and piroxicam are approved for use in JIA. Specific COX-2 inhibitors have not been studied extensively in children and their role is not clearly defined. Aspirin is not recommended in children because of its link with Reye syndrome. There is no evidence to support the use of topical NSAIDs.

Systemic corticosteroids

Systemic steroids (enteral and parenteral) are used to induce remission and maintain disease control in some patients. They have potent anti-inflammatory properties although owing to their significant side-effect profile, efforts should always be taken to minimise long-term exposure.

Intra-articular steroids

Injection of long-acting corticosteroids into the synovial space is a very effective treatment for JIA. As many as two thirds of patients with oligoarthritis have no recurrence of arthritis in an injected joint at two years.³² Joint injections have an important role in oligoarticular disease and may spare the need for any systemic therapy. Significant complications, such as septic arthritis, are exceedingly rare. Mild cosmetic changes including subcutaneous fat atrophy and cutaneous hypopigmentation are seen more frequently.³³ Sedation or general anaesthesia may be required to perform joint injections in some children.

Disease modifying anti-rheumatic drugs (DMARDs)

Systemic disease modifying medications will be required to achieve clinical remission in some patients. Methotrexate is the first-line treatment used for most patients with JIA needing systemic immunosuppressive therapy. It is a highly effective treatment with reassuring long-term safety data.³⁴

Gastrointestinal symptoms such as nausea are common but are usually manageable. Strategies to manage nausea include methotrexate dose reduction, changing to subcutaneous administration, and antiemetic

treatment (ondansetron).³⁵ Serious side effects such as irreversible liver fibrosis, pulmonary fibrosis, malignancy and bone marrow suppression are very rare in children with JIA taking methotrexate.³⁶ Major infections are also uncommon however vigilance is required with regard to this complication. At therapeutic doses, methotrexate is more effective and better tolerated when given by subcutaneous injection rather than orally.³⁷ Folic acid is often given to reduce toxicity without significantly affecting efficacy.³⁸ Regular monitoring including blood count, hepatic enzymes and renal function is required. Patients established on stable doses of the medication need blood tests at least every three months.³⁹

Other medications including leflunomide, sulfasalazine and cyclosporine will be required in some patients with JIA.

Several studies have tried to determine the optimum duration of treatment for patients who achieve sustained inactive disease on treatment.^{40,41} Most clinicians would maintain patients with inactive disease on treatment for at least one to two years before considering a trial of tapering or ceasing systemic medications. The risk of disease flare after ceasing systemic medications is significant and close surveillance is required during this period.

Biologics

Biologic medications have revolutionised the management of JIA by providing effective and tolerable alternatives to other treatments.⁴² They are generally reserved as second-line therapy for patients where treatment with a conventional DMARD has failed. Biologics are potent immunosuppressants that generally target a specific part of the immune system (TNF- α , interleukin-1, interleukin-6, T-cell co-stimulation, CD-20 etc) to regulate the inflammatory process seen in JIA. As with DMARDs, close monitoring is required and duration of treatment is tailored to the patient.

Novel therapies

Emerging treatments including Janus kinase inhibitors have shown great promise in adult rheumatoid arthritis and are likely to be helpful in treating JIA. Phase 1 studies are complete and randomised controlled trials are underway.⁴³

Uveitis

All patients with JIA should have ophthalmology reviews according to

Table 3

Juvenile idiopathic arthritis mimics

Benign

- Growing pains/benign nocturnal limb pain, benign joint hypermobility syndrome

Mechanical and orthopaedic

- Fractures, soft tissue injuries, non-accidental injury, Osgood-Schlatter's disease, Sinding-Larsen-Johansson syndrome, Sever's disease, developmental dysplasia of the hip, Perthe's disease, slipped upper femoral epiphysis, chondromalacia patellae, osteochondrosis dissecans

Infection and infection related

- Osteomyelitis, septic arthritis, reactive arthritis, acute rheumatic fever, post-streptococcal arthritis, transient synovitis of the hip, Lyme disease

Malignancy

- Acute lymphoblastic lymphoma, osteosarcoma, Ewing's sarcoma, neuroblastoma

Haematological

- Sickle cell anaemia, haemarthrosis secondary to bleeding disorders

Inflammatory

- Juvenile dermatomyositis, chronic non-bacterial osteomyelitis, vasculitides (Henoch-Schönlein purpura, Kawasaki disease, systemic lupus erythematosus)

Other

- Chronic regional pain syndrome, chronic widespread musculoskeletal pain, fibromyalgia, functional neurological symptom disorder

key points

SELECTED BY

Dr Chris Barclay
GP, Suffolk, UK

Juvenile idiopathic arthritis (JIA) affects approximately 1-4 per 1,000 children under the age of 16. Girls are more commonly affected than boys. It is a heterogeneous condition, even within JIA categories, ranging from insidious arthritis affecting one to two joints to florid and life-threatening systemic arthritis.

Oligoarticular disease predominantly affects preschool children who are generally otherwise well and remain active despite their arthritis. It typically presents with gradual onset arthritis of the large joints. Polyarticular disease may present with systemic symptoms, such as lethargy, malaise and even low-grade fever, and tends to affect multiple large and small joints symmetrically. Systemic onset JIA on the other hand can cause prolonged fever accompanied by a macular rash. Arthritis may be a relatively late clinical finding. Evidence of immune activation may be seen. A small percentage of patients with systemic onset JIA will experience macrophage activation syndrome. This severe, uncontrolled immune response is a medical emergency with significant mortality rates.

Uveitis affects up to 20% of patients with JIA. It is usually asymptomatic in the early stages and may precede the onset of arthritis. It can be sight threatening if not detected and treated. Some clinical signs such as cataracts, keratic precipitates, and irregular pupils secondary to synechiae can be observed by direct ophthalmoscopy. Patients should have an ophthalmic assessment within six weeks of initial diagnosis or urgently if any eye signs or symptoms are present.

All patients with suspected JIA should be referred urgently to a specialist paediatric rheumatology team. Coordinated, multidisciplinary care within a specialist team is required to achieve optimal outcomes. Most patients with JIA will need rheumatology follow-up into adulthood and transition to adult services usually occurs between 16 and 18 years of age. Planned and coordinated transition is vital for ensuring continuity of care.

Early, aggressive therapy increases the likelihood of a response to first-line treatments and of achieving drug-free remission later in life. NSAIDs are used first line for symptomatic treatment. Systemic steroids are used to induce remission and maintain disease control in some patients. Systemic disease modifying medications (e.g. methotrexate, leflunomide, sulfasalazine and cyclosporine) will be required in some cases. Biologic medications are generally reserved as second-line therapy should conventional DMARDs fail. Patients on systemic immunosuppressive therapy are at risk of severe infection. Symptoms may be masked by treatments. Any sign of infection should prompt urgent medical review and early initiation of treatment if needed.

Table 4

Vaccinations in patients with juvenile idiopathic arthritis

Non-live vaccines should be given to all patients according to local guidelines

Live attenuated vaccines (including measles, mumps, rubella, BCG, varicella zoster, yellow fever, oral poliovirus, rotavirus) should generally be withheld for all patients on high-dose immunosuppressive therapy such as:

- Glucocorticoids (prednisolone equivalent ≥ 2 mg/kg or ≥ 20 mg/day) for ≥ 2 weeks or intravenous pulse steroid therapy
- Methotrexate > 15 mg/m²/week
- Sulfasalazine > 40 mg/kg/day or 2 g/day
- Leflunomide > 0.5 mg/kg/day
- Biologic DMARDs at any dose

local guidelines. The most frequent cause of avoidable morbidity is missed or inadequate examinations in the first year of disease. Each patient should have a formal ophthalmic assessment within six weeks of initial diagnosis or urgently if any eye signs or symptoms are present.⁴⁴

Systemic therapies for JIA often concurrently treat uveitis. However, some patients require treatment escalation specifically for their eye disease.^{45,46} Treatment options include local corticosteroids, methotrexate and biologics.^{47,48,49}

Vaccination and infections

Non-live vaccinations should be given to all patients with JIA according to local guidelines although it is worth noting that immunogenicity may be impaired if vaccines are given while the patient is on immunosuppressive treatment.⁵⁰ Live vaccines should generally be withheld while on high-dose therapy, see table 4, above, but can be considered on a case by case basis weighing the risk of infection against the hypothetical risk of inducing infections by vaccination.

Annual influenza vaccination should be considered in all patients. If not already immune, children should ideally be vaccinated against varicella before starting systemic immunosuppressive treatment. Patients on systemic immunosuppressive therapy are at risk of severe infection and symptoms may be masked by treatments. Any sign of infection should prompt urgent medical review and early initiation of treatment if needed. Varicella contact or disease in children on systemic immunosuppressive therapy should prompt consideration of treatment with zoster immunoglobulin or anti-viral agents.⁵¹

Transition

Most patients with JIA will need rheumatology follow-up into adulthood

and transition to adult services usually occurs between 16 and 18 years of age. Planned and coordinated transition is vital for ensuring continuity of care.^{52,53}

CONCLUSION

The long-term outlook for patients with JIA has markedly improved over recent decades. Severe morbidity and mortality were not uncommon prior to the introduction of contemporary treatments.⁵⁴ Therapeutic advances have drastically changed the lives of patients with this condition.⁴² Most patients will achieve clinically inactive disease and many, particularly those with oligoarticular disease, will attain long-term remission off medications.⁵⁵

Despite these advances, substantial long-term effects in terms of reduced quality of life, physical function, mental health, growth and development are frequently reported.⁵⁶⁻⁵⁹ Sequelae from chronic ocular inflammation remain a major source of morbidity.⁶⁰

Competing interests: None

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Useful information

Arthritis Research UK

Information and support for patients and their families
www.arthritisresearchuk.org/arthritis-information/conditions/juvenile-idiopathic-arthritis.aspx

JIA-at-NRAS

Information and support for patients and their families
www.jia.org.uk

Olivia's Vision

Support group for uveitis sufferers
www.oliviasvision.org

PRINTO

Paediatric Rheumatology International Trials Organisation
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editor@thepractioner.co.uk

Show impact

- Collection of data
- Practice audit to show improved care

- Case studies
- Implement a protocol
- Prescribing review
- Educational meetings
- Significant event audit
- Practice meeting
- Implement a new service
- Take on new role
- Significant event audits
- Change with feedback from patients and/or colleagues

Further options for sessional GPs

- Self audit of own practice:
 - Record-keeping
 - Referrals for investigations
 - Prospective condition based reviews
 - Random case analysis with colleagues
 - Review of telephone triage outcomes
- Update drugs in emergency bag

Time credits

Impact credits
Quick impact

Later impact

Later
impact=

Total credits

Title and reference

Date

What have you learned?

How will this change your practice?

What research/actions will you take that will have further impact on practice?

Draft of your action plan

CPD prompt and framework Case review			
Clinical case for review		Summary of any discussion of the case with peers	
Reason for selection of the case for reflection		What changes/actions have resulted to your personal practice?	
Evidence base used to reflect on your practice		What changes/actions have resulted to the practice?	
What went well?		How/when will you review these changes?	
What could have been done better?			
What were the causes of the condition/event?			
What learning needs arise from this case for (a) you and (b) for the practice?			
		Time creditsImpact creditsTotal credits	

Title

Reflection on Table 1 results

Reason for the audit (target to improve or implement)

Define criterion (or criteria) to be met

What changes were implemented to improve results?

Set the standard and its basis

Reflection on Table 2 results and review with peers

Plan the audit process and any involvement of peers

Time credits

Impact credits

Total credits

Table 1			
Results of data 1 analysis		Date of data collection:	
Criterion	Number sampled	Achievement (%)	Standard (%)
A			
B			
C			

Table 2					
Results of data 1 and data 2 analyses			Date of data collection:		
Criterion	Number sampled Data 1	Achievement (%) Data 1	Number sampled Data 2	Achievement (%) Data 2	Standard (%)
A					
B					
C					