New Medicine Assessment

Ketamine for Chronic Non-Cancer Pain (off-label use) in adults

Recommendation for infusion/injection: Black

Not recommended for use in the NHS in Lancashire and South Cumbria.

Ketamine administered via infusion/injection or when administered orally is not recommended to treat patients with chronic refractory pain (pain unresponsive to both non-pharmacological therapies and four or more conventional drug therapies). Evidence of efficacy is limited and mostly examines acute use of the drug.

Recommendation for oral use: Red

Primary care prescribing is not recommended. These treatments should be initiated by specialists only and prescribing retained within NHS commissioned specialist pain services in Lancashire and South Cumbria.

Oral ketamine is supported for the treatment of chronic non-cancer pain in a small number of patients after assessment by and under the care of some NHS commissioned specialist pain services, where other standard treatments have been unsuccessful and is subject to ongoing regular specialist review. This guidance only applies to patients being treated in an NHS commissioned service.

Summary of supporting evidence:

- The use of ketamine infusions and oral ketamine to manage chronic pain is unlicensed and there are uncertainties around the efficacy and safety of ketamine in the proposed indication.
- A Systematic review of high methodological quality found IV ketamine provides significant short-term analgesic benefit in patients with refractory chronic pain, with some evidence of a dose–response relationship. [1]
- A randomised controlled trial found that intravenous ketamine significantly reduced pain compared to placebo in chronic pain patients who experienced acute exacerbation within 60 minutes of treatment, but the analgesic effect of ketamine was not observed at 24 to 48 hours of follow-up. [2]
- The “Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists” supports the use of ketamine for chronic pain, but the level of evidence varies by condition and dose range. [3]
- Studies of oral ketamine recruited small patient numbers in limited pain indications for short follow up periods. Cohen et al concluded that oral ketamine has poor bioavailability, and the relative dosages used in these studies were considerably less than in the studies evaluating IV administration. [3]

Date: February 2023

Details of Review

Name of medicine (generic & brand name)**:**

Ketamine (Ketalar). [4]

Strength(s) and form(s):

10 mg/ml and 50 mg/ml solution for injection.

50 mg/5 ml oral solution (Unlicensed special)

50 mg/5 ml oral suspension (Unlicensed special)

Dose and administration:

Intravenous infusion (off-label)

Based on data from clinical trials ketamine doses ranged between 0.2 to 0.6 mg/kg/hour, infusing continuously or intermittently (unlicensed use). [4]

Oral (unlicensed)

Based on data from clinical trials ketamine doses ranged between 0.5 to 4 mg/kg or 20 to 100mg either in a single dose or divided doses

BNF therapeutic class / mode of action:

Anaesthetics / NMDA receptor antagonist.

Licensed indication(s):

As an anaesthetic agent for diagnostic and surgical procedures.

For the induction of anaesthesia prior to the administration of other general anaesthetic agents.

To supplement other anaesthetic agents.

Proposed use (if different from, or in addition to, licensed indication above):

Chronic Non-Cancer Pain.

Course and cost:

IV infusions:

10 mg/ml, 1×20 ml solution for injection vial=£5.06

50 mg/ml, 1×10 ml solution for injection vial=£8.77

Dose: 0.2 mg/kg/hr to 0.6 mg/kg/hr X 76 (average body weight) X 1 (duration of infusion in hours) = 15.2 mg to 45.6 mg

Cost per infusion assuming 20mg/ml vial used (no vial sharing), body weight of 76kg and dose range of 0.2 to 0.6 mg/kg administered over 1 hour would be the cost of a single vial £5.06 plus the tariff cost for a day attendance £517. The approximate total cost would be **£522**.

Assuming that a patient needed 3-5 repeated infusion per year the annual cost would be **£1566 to £2610.**

Oral ketamine:

Ketamine 50 mg/5 ml oral solution: £61.33 for minimum volume of 200 ml plus £0.01 for

each extra ml.

Ketamine 50 mg/5 ml oral suspension: £47.23 for minimum volume of 200 ml plus £0.06 for each extra ml.

Dose: 0.5 to 4 mg/kg daily for average body weight (76 kg) = 38 to 304 mg daily (1,140 mg to 9,120 mg required every 30 days).

30 days treatment would require 114 ml to 912 ml of 50 mg/ml suspension

Cost for 30 days treatment of 50mg/ml oral suspension:

Minimum cost for 114 ml = £47.23 (i.e. one 200 ml bottle of 50mg/5ml suspension assuming 30-day expiry)

Maximum cost for 912 ml = £47.23 (for the first 200 ml) + £42.72 (712 ml at £0.06 per ml) = £89.95

Annual cost per patient = £47.23 to £89.95 x 12 = £566.76 to £1079.40

(NB – small savings are possible if ketamine solution for injection is taken orally off-label as an alternative to oral suspension)

Current standard of care/comparator therapies:

It is expected that ketamine infusion would be a treatment following failure of multiple therapies. There are no pharmacological comparator treatments at this stage of therapy.

Relevant NICE guidance:

N/A

Background and context

Chronic pain is a persistent pain (duration longer than 12 weeks), which continues after healing or is the result of ongoing damage and includes spinal pain, post-traumatic pain (e.g. after amputation or surgery), pain involving the central or peripheral nervous system (e.g. post stroke pain, complex regional pain syndrome, diabetic neuropathy, post herpetic neuralgia and sciatica) and pain associated with other chronic diseases such as angina, arthritis, endometriosis, headache and pancreatitis. Chronic Pain is also recognised as a long-term Condition in its own right. 6-8% of the population have severe chronic pain that prevents some or most activities. [5]

The management of chronic pain is complex, often requiring a multidisciplinary approach using a wide range of both pharmacological and non-pharmacological management strategies. Chronic pain management should focus on non-pharmacological strategies just as much as the use of analgesic drugs. The prescription of medication is the most convenient element of care but is potentially the most harmful and sometimes the least effective. [6]

Injectable ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist is licensed in the UK as an anaesthetic agent for diagnostic and surgical procedures in children, young people and adults. It is not currently licensed in the UK for treating chronic pain. The LSCMMG received a request from East Lancashire CCG to review the use of ketamine infusions for the management of fibromyalgia following identification of a number of patients receiving repeated infusions from private hospitals in their locality.

Following discussions about the use of ketamine infusions at the October 2020 meeting of the

LSCMMG, the group requested unlicensed oral ketamine administration to be considered in the scope of this review.

Summary of evidence

Summary of efficacy data in proposed use:

There is a paucity of studies for the use of ketamine infusion and oral ketamine in specific types of chronic pain. A Canadian review of efficacy and safety of ketamine has been used to inform this review. The review carried out by The Canadian Agency for Drugs and Technologies in Health (CADTH) provides Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in the Canadian health care system.

The population included in this review pooled patients with various types of chronic non-cancer pain e.g. neuropathic pain, complex regional pain syndrome and degenerative disc disease.

Evidence for IV infusion use

CADTH 2020 Review [7]

This review included two systematic reviews (SRs) [1] [8] and two randomised controlled trials (RCTs) [2] [9] of the clinical effectiveness of ketamine for treating patients with chronic non-cancer pain. Both included SRs were comprised of only RCTs. One SR [1] synthesized data using meta-analysis, while the other SR [8] narratively described the findings of its included studies. Both included RCTs were single-centre, blinded, parallel RCTs, with data analysed using the modified intention-to-treat approach.

One SR [1] included seven RCTs (N = 211; ranging from 19 to 60 participants) having adult patients with chronic pain for more than three months, including phantom limb pain, post-spinal cord injury pain, complex regional pain syndrome (CRPS) types I and II, cancer related pain, fibromyalgia, and ischemic limb pain. The SR did not include data of the trial involving cancer related pain in the meta-analysis of primary endpoint due to lack of standard deviation. The other SR [8] included 21 RCTs (N = 456; ranging from 8 to 92 participants) evaluating ketamine treatment in adult patients with neuropathic pain. The primary outcome considered in both SRs was pain. Visual analogue scale (VAS) either on 0 to 10 scale (0 = no pain and 10 = worst pain) or 100-mm scale (0 = no pain and 100 = worst pain) was used to assess pain.

One RCT [2] included adult patients (N = 97; mean age = 46.5 years) presented to the emergency department (ED) with acute exacerbation from chronic pain. The other RCT [9] included adult patients (N = 147; mean age = 56 years) with chronic pain who underwent lumbar fusion surgery.

Orhurhu et al (2019) SR [1]

This review included RCTs that compared intravenous (IV) ketamine with placebo. The median dose of ketamine was 0.35 mg/kg (range, 0.23 to 0.6 mg/kg), which was infused continuously or intermittently. The median duration of infusion was five hours (range, 0.5 to 100 hours). The median number of days of infusion was one day (range, 1 to 10 days).

The meta-analysis of data from six RCTs showed that IV ketamine infusions significantly reduced pain scores between 48 hours and two weeks after treatment compared to placebo in patients with various chronic pain. Subgroup analyses revealed that there were no significant differences in terms of dose response (i.e., high versus low), types of pain (neuropathic versus non-neuropathic; CRPS versus without CRPS), and adjunct medication (with versus without). Subgroup analysis regarding different time points revealed that administration of IV ketamine resulted in a significant reduction in pain scores when compared to placebo at 2 weeks after treatment, but not at longer time points.

Meta-analysis of data from three included RCTs showed that patients treated with IV ketamine compared with placebo achieved higher positive response rate, defined as reduction in pain scores by ≥ 30% or ≥ 50% from baseline to 48 hours or longer after intervention. [7]

Aiyer et al (2018) SR [8]

The review included trials investigating the efficacy of N-methyl-D-aspartate (NMDA) receptor antagonists for neuropathic pain, of which 21 trials involving ketamine that compared ketamine of different formulations (three oral, five topical and 13 IV trials) with placebo. The IV ketamine dose ranged between 0.2 to 0.6 mg/kg/hour, infusing continuously or intermittently. Treatment duration was not reported in the SR for every trial.

All 13 RCTs with IV ketamine showed a significant improvement in pain in various conditions, including chronic neuropathic pain, CRPS, chronic phantom limb pain, peripheral nerve injury, and spinal cord injury. The duration of ketamine effect was not reported in this SR. [7]

Lumanauw et al (2019) RCT [2]

In this RCT, three treatment groups compared IV ketamine 0.5 mg/kg, IV ketamine 0.25 mg/kg and placebo. Infusion time was 20 minutes. The outcomes considered were pain reduction of at least 20 mm in 100-mm of the visual analogue scale (VAS), and adverse events. Pain and adverse events were assessed at 20, 40 and 60 minutes. Patients were followed up by telephone at 24 to 48 hours following discharge from the ED to assess persistent or recurrent pain using a numeric rating scale (0 to 10; 0 = no pain and 10 = worst pain).

IV ketamine for treatment of acute exacerbation from chronic pain resulted in a significantly higher positive response rate compared to placebo within 60 minutes of treatment in the RCT. Positive response was defined as VAS pain reduction by 20 mm over the course of the study. There was no significant difference in pain relief between high (0.5 mg/kg) and low (0.25 mg/kg) ketamine doses. During follow-up at 24 to 48 hours, there was no significant difference in pain scores between three groups.

Nielsen et al (2017) RCT [9]

In this RCT, the outcomes were cumulated patient-controlled analgesia IV morphine consumption from 0 to 24 hours after surgery, pain at rest and during mobilisation from recumbent position to sitting bedside, and adverse events (i.e., nausea and sedation). Pain was evaluated using 100-mm VAS at 2, 6, 12, 18, and 24 hours after surgery. IV ketamine had no significant difference in pain scores compared with placebo during mobilisation or at rest when assessed at 2 to 24 hours postoperatively. There was also no significant difference in persistent pain between IV ketamine and placebo assessed six months after surgery although IV ketamine was associated with a significant reduction in cumulated patient-controlled analgesia IV morphine consumption from 0 to 24 hours after surgery.

Evidence for oral ketamine use

Aiyer et al (2018) SR [8]

The review (described above) included trials investigating the efficacy of N-methyl-D-aspartate (NMDA) receptor antagonists for neuropathic pain. Of these RCTs, assessed the use of oral ketamine. The oral doses used in the RCTs were 30 mg three times a day, 0.5 mg/kg every 6 hours for one week, or 20 mg increasing to maximum 100 mg. Of the 3 RCTs with oral ketamine included in the review, only one small RCT (N = 42; 14 participants per group) found that ketamine alone significantly improved chronic neuropathic pain compared with both methadone or combination of methadone and ketamine groups.

Other efficacy data:

IV infusions

Michelet et al (2018) SR [10]

This meta-analysis of clinical trials compared ketamine to a placebo during chronic non-cancer pain. The primary endpoint of this study was pain relief 4 weeks after the beginning of treatment. Six studies were included in this meta-analysis including all routes of ketamine administration (IV, oral, topical, intranasal). Overall, 99 patients received ketamine and 96 received placebo. Ketamine did not decrease pain intensity at 4 weeks (MD (on a 0 to 10 scale) = -1.12 [-2.33, 0.09], GRADE evidence: very low). However, analysing studies with no high-risk bias found ketamine to decrease pain intensity at 4 weeks and increased the level of GRADE evidence to moderate.

Oral Ketamine

Rabben et al (1999) RCT [11]

Participants were initially randomised to a single dose of either intramuscular ketamine and midazolam, or pethidine, and crossed over to the alternative treatment after 1 week. After another week, 26 participants were randomised to 4 mg/ kg oral ketamine (prepared capsules) or placebo once daily at bedtime for 3 days (to see if pain was reduced on the days after ketamine was given), and then crossed over to the alternative treatment. Most participants were reported to have been treated previously with drugs and procedures without effect or with minimal temporary effect. Five of 26 participants (19.2%) experienced reduced pain (not further defined) on the days after oral ketamine was given at bedtime. Significance testing between oral ketamine and placebo was not reported. [12]

Summary of safety data:

Common ketamine-related adverse outcomes reported in the trials included nausea, vomiting, psychotomimetic effects, headache, fatigue, and sedation. Compared to placebo, the ketamine group had significantly higher relative risk of nausea and psychotomimetic effects. The relative risk of headache and tiredness was higher among the ketamine group, but the differences were not statistically significant. Nausea and vomiting were also higher in the ketamine group, but this was reported by one study. [1] The limited trial data for the use of oral ketamine reported similar adverse events to those described in the SPC for ketamine injection e.g. headache, drowsiness and dizziness.

The SPC for ketamine injection reports the adverse effects when used as an anaesthetic (higher doses than used in pain). The full list of adverse events is tabulated below: [4]

Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Not known (frequency cannot be estimated from the available data)

MedDRA System Organ Class	Frequency	Undesirable Effects
Immune system disorders	Rare	Anaphylactic reaction
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Common	Hallucination, Abnormal dreams, Nightmare, Confusion, Agitation, Abnormal behaviour
	Uncommon	Anxiety
	Rare	Delirium, Flashback, Dysphoria, Insomnia, Disorientation
Nervous system disorders	Common	Nystagmus, Hypertonia, Tonic clonic movements
Eye disorders	Common	Diplopia
	Not Known	Intraocular pressure increased
Cardiac disorders	Common	Blood pressure increased, Heart rate increased

	Uncommon	Bradycardia, Arrhythmia
Vascular disorders	Uncommon	Hypotension
Respiratory, thoracic and Mediastinal disorders	Common	Respiratory rate increased
	Uncommon	Respiratory depression, Laryngospasm
	Rare	Obstructive airway disorder, Apnoea
Gastrointestinal disorders	Common	Nausea, Vomiting
	Rare	Salivary hypersecretion
Hepatobiliary disorders	Not known	Liver function test abnormal, Drug-induced liver injury
Skin and subcutaneous tissue disorders	Common	Erythema, Rash morbilliform
Renal and urinary disorders	Rare	Cystitis, Haemorrhagic cystitis
General disorders and administration site conditions	Uncommon	Injection site pain, Injection site rash

Contraindications and cautions

Ketamine is contra-indicated in persons with hypersensitivity to the active substance or to any of the excipients, and in persons in whom an elevation of blood pressure would constitute a serious hazard. Ketamine should not be used in patients with eclampsia or pre-eclampsia, severe coronary or myocardial disease, cerebrovascular accident or cerebral trauma. Safety has not been established in pregnancy and lactation.

Patients should be cautioned that driving a car, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more after anaesthesia (although this may also be relevant to doses used in pain relief).

Ketamine should be used with caution in patients with chronic alcoholic syndrome and the acutely alcohol-intoxicated patient. Ketamine is metabolised in the liver and hepatic clearance is required for termination of clinical effects. A prolonged duration of action may occur in patients with cirrhosis or other types of liver impairment. Dose reductions should be considered in these patients. Abnormal liver function tests associated with ketamine use have been reported, particularly with extended use (>3 days) or drug abuse.

Use with caution in patients with intracranial mass lesions, a presence of head injury, or hydrocephalus, globe injuries and increased intraocular pressure (e.g. glaucoma) because the pressure may increase significantly after a single dose of ketamine. Caution is required in patients with neurotic traits or psychiatric illness (e.g. schizophrenia and acute psychosis), acute intermittent porphyria, seizures, pulmonary or upper respiratory infection (ketamine sensitises the gag reflex, potentially causing laryngospasm), hyperthyroidism or patients receiving thyroid replacement (increased risk of hypertension and tachycardia).

Because of the substantial increase in myocardial oxygen consumption, ketamine should be used in caution in patients with hypovolemia, dehydration or cardiac disease, especially coronary artery disease (e.g. congestive heart failure, myocardial ischemia and myocardial infarction). In addition, ketamine should be used with caution in patients with mild-to-moderate hypertension and tachyarrhythmias.

Long-Term Use

Cases of cystitis including haemorrhagic cystitis, acute kidney injury, hydronephrosis, and ureteral disorders have been reported in patients being given ketamine on a long-term basis, especially in the setting of ketamine abuse. These adverse reactions develop in patients receiving long term ketamine treatment after a time ranging from 1 month to several years. **Ketamine is not indicated nor recommended for long term use.** Hepatotoxicity has also been reported in patients with extended use (> 3 days).

Drug Abuse and Dependence

Ketamine has been reported as being a drug of abuse. Reports suggest that ketamine produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia, or disorientation. Ketamine dependence and tolerance may develop in individuals with a history of drug abuse or dependence. Therefore, ketamine should be prescribed and administered with caution. The risk of abuse and diversion is particularly important in those patients who are supplied oral ketamine preparations.

Interactions

The use of ketamine with other central nervous system (CNS) depressants (e.g. ethanol, phenothiazines, sedating H_1 – blockers or skeletal muscle relaxants) can potentiate CNS depression and/or increase risk of developing respiratory depression. Reduced doses of ketamine may be required with concurrent administration of other anxiolytics, sedatives and hypnotics.

Patients taking thyroid hormones have an increased risk of developing hypertension and tachycardia when given ketamine. Concomitant use of antihypertensive agents and ketamine increases the risk of developing hypotension. Sympathomimetics (directly or indirectly acting) and vasopressin may enhance the sympathomimetic effects of ketamine. Concomitant use with ergometrine may lead to an increase in blood pressure. When ketamine and theophylline or aminophylline are given concurrently, a clinically significant reduction in the seizure threshold may be observed. Unpredictable extensor-type seizures have been reported with concurrent administration of these agents.

Drugs that inhibit/induce CYP3A4 enzyme activity generally decrease/increase hepatic clearance, resulting in increased/decreased plasma concentration of CYP3A4 substrate medications, such as ketamine. Coadministration of ketamine with drugs that inhibit/induce CYP3A4 enzyme may require a decrease/increase in ketamine dosage to achieve the desired clinical outcome.

Strengths and limitations of the evidence:

Strengths

- A Systematic review of high methodological quality found IV ketamine provides significant short-term analgesic benefit in patients with refractory chronic pain, with some evidence of a dose–response relationship. [1]
- A randomised controlled trial found that intravenous ketamine significantly reduced pain compared to placebo in chronic pain patients who experienced acute exacerbation within 60 minutes of treatment, but the ketamine analgesic effect was not observed at 24 to 48 hours of follow-up. [2]
- The “Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists” supports the use of ketamine for chronic pain, but the level of evidence varies by condition and dose range. [3]
- Overall, the consensus guideline group concluded that there is low-level evidence to support the use of oral ketamine (150 mg/d or 0.5 mg/kg every 6 hours) as follow-up therapy following IV infusions. [3]

Limitations

- The use of ketamine infusions and oral ketamine to manage chronic pain is unlicensed and there are uncertainties around the efficacy and safety of ketamine in the proposed indication.
- Serious hepatic and genitourinary adverse events have been reported with ketamine use for other indications.
- Ketamine is known as a drug of abuse and there may be at risk of abuse or diversion if

supplied to patients in primary care.

- Most studies evaluating the efficacy of ketamine were small and uncontrolled and were either unblinded or ineffectively blinded. [3]
- A CADTH review concluded that IV ketamine compared to placebo could only provide significant **short-term** pain relief in patients with chronic non-cancer pain. [7]
- The CADTH review also concluded that oral ketamine was not efficacious for the treatment of neuropathic pain. [7]
- The randomised controlled trials for IV ketamine included in the systematic reviews only recruited small patient numbers and follow up periods were short.
- Studies of oral ketamine recruited small patient numbers in limited pain indications for short follow up periods. Cohen et al concluded that oral ketamine has poor bioavailability, and the relative dosages used in these studies were considerably less than in the studies evaluating IV administration. [3]
- No economic studies have been published to evaluate the cost-effectiveness of ketamine infusions.

Summary of evidence on cost effectiveness:

N/A

Prescribing and risk management issues:

To be used only in hospitals by or under the supervision of experienced medically qualified anaesthetists except under emergency conditions.

Ketamine dependence and tolerance may develop in individuals with a history of drug abuse or dependence. Therefore, ketamine should be prescribed and administered with caution.

Innovation, need and equity implications of the intervention:

Ketamine provides an additional treatment option for patients with refractory pain (pain unresponsive after four or more conventional drug therapies) or patients failing on opioids.

Financial implications of the intervention:

The existing use of ketamine infusions for the management of chronic pain in Lancashire and South Cumbria is believed to be low and it is not anticipated that updated guidance would cause a significant surge in treatments. However, estimation of exact patient numbers is not possible.

Approximating 50 patients as a lower limit and 100 as an upper the limit for the number of patients treated annually the approximate cost range would be:

Annual cost (£1566 to £2610) X number of patients (50 to 100) = **£78,300 to £261,000**

There has been no prescribing of any ketamine products in primary care in the last twelve months to November 2020. It is therefore highly likely that patient numbers eligible for ketamine oral formulations will be negligible. The estimated cost for every 10 patients treated with ketamine oral suspension would be as follows:

Annual cost (£566.76 to £1079.40) X number of patients (10) = **£5,668 to £10,794**

(NB – a updated RAG status could result in greater patient numbers than the above estimates).
Service Impact Issues Identified:
As multiple infusions may be required annually, each additional patient treated may require more appointments with specialist services than they may have otherwise required. Administration of additional infusions is likely to place additional burdens on specialist services. Ketamine is a schedule 2 controlled drug which requires regular prescribing and reviewing. Patients receiving oral ketamine in primary care after stabilisation in specialist settings will require regular monitoring for cardiovascular and respiratory effects, sedation levels and cystitis or ureteral disorders.
Equality and Inclusion Issues Identified:
Include the summary of the outcome of the screening tool.
Cross Border Issues Identified:
IV Ketamine for chronic pain has a “Red” RAG classification meaning that it may be considered for prescribing by specialist/hospital services. Ketamine oral solution has an “Amber Retained” RAG classification meaning that it may be prescribed in primary care, but patients should not be discharged from specialist care. The GMMMG has a “Red” RAG classification for ketamine in chronic pain management (no route or formulation specified). Oral ketamine solution has a separate entry recommending a “Red” RAG for specialist use only, for short term use as an opioid-sparing agent.
Legal Issues Identified:
N/A
Media/ Public Interest:
N/A

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Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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