

# Chronic pain: oral ketamine

## Evidence summary

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[nice.org.uk/guidance/esuom27](https://www.nice.org.uk/guidance/esuom27)

## Key points from the evidence

The content of this evidence summary was up-to-date in February 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), [BNF for children \(BNFc\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

Two small, short-term, randomised, placebo-controlled trials and 1 small case series of n-of-1 trials provide no good quality evidence for the use of oral ketamine to treat chronic pain in adults. Only 1 phase I pilot study in young people was identified but this was too small and short-term to draw any firm conclusions about the efficacy and safety of oral ketamine for treating chronic pain in young people. In the studies that reported safety, oral ketamine was frequently associated with adverse effects that often resulted in treatment discontinuation.

**Regulatory status:** unlicensed if oral liquid preparations (as prepared by 'specials' manufacturers) are used, or off-label if the solution for injection or infusion is used orally (different indication and route to the licence). Ketamine is controlled as a class B drug under the Misuse of Drugs Act 1971, and as a schedule 4, part 1 drug under the Misuse of Drugs Regulations 2001, but its scheduling is currently subject to review (see [regulatory status of oral ketamine](#)).

The topic was prioritised because of the high volume of requests from the NHS for information on this topic and the potential for variation in practice.

<p><b>Effectiveness</b></p> <ul style="list-style-type: none"><li>• Two small, short-term, randomised, placebo-controlled trials and 1 small case series of n-of-1 trials provide insufficient evidence for using oral ketamine for treating chronic pain in adults.</li><li>• Only 1 small, short-term phase I pilot study was identified that assessed the efficacy and safety of oral ketamine for treating chronic pain in young people. It found that oral ketamine improved pain scores without causing dose-limiting adverse effects in 5 out of 12 people taking between 0.25 and 1 mg/kg per dose. The small number of participants and short treatment duration (2 weeks) limit the conclusions that can be drawn.</li></ul>	<p><b>Safety</b></p> <ul style="list-style-type: none"><li>• Adverse effects were frequently reported with oral ketamine in the randomised controlled trials, and case series in adults.</li><li>• In the pilot phase I study in young people, 2 participants out of 12 experienced a dose-limiting toxicity with oral ketamine at 1.5 mg/kg per dose.</li><li>• Common adverse effects listed in the summary of product characteristics for ketamine hydrochloride injection (<u>Ketalar</u>, licensed as an anaesthetic agent for diagnostic and surgical procedures in children, young people and adults) include hallucination, abnormal dreams or nightmares, confusion, agitation, abnormal behaviour, nystagmus, hypertonia, tonic clonic movements, diplopia, increased blood pressure, heart rate or respiratory rate, nausea, vomiting, erythema and morbilliform rash.</li><li>• Cases of cystitis, including haemorrhagic cystitis, have been reported in people being given ketamine on a long-term basis; therefore the summary of product characteristics states that 'ketamine is not indicated nor recommended for long term use'.</li></ul>
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Patient factors	Resource implications
<ul style="list-style-type: none"> <li>• Withdrawal rates because of adverse effects are high. In the case series of n-of-1 trials, almost half of all participants withdrew from the study with oral ketamine because of adverse effects.</li> <li>• Ketamine is known as being a drug of abuse, with reports suggesting that it produces a variety of symptoms, including flashbacks, hallucinations, dysphoria, anxiety, insomnia and disorientation. If used on a daily basis for a few weeks, dependence and tolerance may develop, particularly in people with a history of drug abuse and dependence.</li> </ul>	<p>Ketamine hydrochloride solution for injection or infusion (<u>Ketalar</u>, Pfizer) costs:</p> <ul style="list-style-type: none"> <li>• 10 mg/ml, 1×20 ml vial=£5.06</li> <li>• 50 mg/ml, 1×10 ml vial=£8.77</li> <li>• 100 mg/ml, 1×10 ml vial=£16.10</li> </ul> <p>The cost of ketamine oral liquid preparations varies depending on the strength, quantity and supplier. Standard costs are listed in Part VIIB of the drug tariff for the 2 following formulations:</p> <ul style="list-style-type: none"> <li>• Ketamine 50 mg/5 ml oral solution: £215.90 for minimum volume of 200 ml plus £0.01 for each extra ml.</li> <li>• Ketamine 50 mg/5 ml oral suspension: £132.25 for minimum volume of 200 ml plus £0.01 for each extra ml.</li> </ul>

## Key points

Ketamine (in any preparation) is not currently licensed in the UK for treating chronic pain in children, young people or adults.

Ketamine hydrochloride solution for injection or infusion (Ketalar, Pfizer) is licensed in the UK as an anaesthetic agent for diagnostic and surgical procedures in children, young people and adults.

Oral liquid preparations of ketamine are not licensed in the UK, so use of these preparations, which are prepared by 'specials' manufacturers, is unlicensed. When ketamine solution for injection or infusion is used orally, this is off-label use.

Two small (n=26 and n=8), placebo-controlled randomised controlled trials (RCTs), and 1 small case series of n-of-1 trials (n=9) do not provide sufficient or reliable evidence of the short-term or long-term efficacy or safety of oral ketamine in adults with chronic pain. These studies were short-term (ranging from 3 days to 6 weeks), so the longer-term efficacy and safety of oral ketamine for treating chronic pain in adults cannot be determined.

No RCTs were identified that assessed oral ketamine for treating chronic pain in children or young people. One small phase I pilot study in young people found that 5 out of 12 people had reduced pain without dose-limiting adverse effects while receiving oral ketamine (0.25 to 1.0 mg/kg per dose).

Oral ketamine was frequently associated with adverse effects in a long-running case series. In the case series of n-of-1 trials assessing the short-term use of oral ketamine, 12 out of 21 participants discontinued treatment with oral ketamine during an initial 1-week open-label run-in because of no benefit and / or intolerable adverse effects.

In 2012 the Advisory Council on the Misuse of Drugs reviewed the misuse and harms of ketamine and in December 2013 it [recommended](#) that ketamine be upgraded to a class B and, subject to the outcome of a public consultation, a Schedule 2 drug, following increased evidence of bladder damage from frequent misuse (see [regulatory status of oral ketamine](#)).

On 10 June 2014, the [Parliamentary Order](#) reclassifying ketamine as a class B drug came into force. Ketamine is not being rescheduled immediately. In line with the Advisory Council on the Misuse of Drugs' (ACMD) advice, the Home Office will carry out a public consultation later this year to assess the impact of rescheduling ketamine to Schedule 2. A final decision on the appropriate schedule for ketamine will be made after the consultation. Until then ketamine will remain a Schedule 4 Part 1 drug (see the [Medicines and Healthcare Products Regulatory Agency Medicines regulatory news on the control of lisdexamphetamine, tramadol, zaleplon, zopiclone and reclassification of ketamine](#) for more information).

#### About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

## Overview for healthcare professionals

### *Regulatory status of oral ketamine*

Ketamine (in any preparation) is not currently licensed in the UK for treating chronic pain in children, young people or adults.

Ketamine hydrochloride solution for injection or infusion ([Ketalar](#), Pfizer) is licensed in the UK as an anaesthetic agent for diagnostic and surgical procedures in children, young people and adults.

Oral liquid preparations of ketamine are not licensed in the UK, so use of these preparations, which are prepared by 'specials' manufacturers, is unlicensed. When ketamine solution for injection or infusion is used orally, this is off-label use.

In 2012 the Advisory Council on the Misuse of Drugs reviewed the misuse and harms of ketamine and in December 2013 it [recommended](#) that ketamine be upgraded to a class B and, subject to the outcome of a public consultation, a Schedule 2 drug, following increased evidence of bladder damage from frequent misuse (see [regulatory status of oral ketamine](#)). On 10 June 2014, the Parliamentary Order reclassifying ketamine as a class B drug came into force. Ketamine is not being rescheduled immediately. In line with the Advisory Council on the Misuse of Drugs' (ACMD) advice, the Home Office will carry out a public consultation later this year to assess the impact of rescheduling ketamine to Schedule 2. A final decision on the appropriate schedule for ketamine will be made after the consultation. Until then ketamine will remain a Schedule 4 Part 1 drug (see the [Medicines and Healthcare Products Regulatory Agency Medicines regulatory news on the control of lisdexamphetamine, tramadol, zaleplon, zopiclone and reclassification of ketamine](#) for more information).

In line with [prescribing guidance from the General Medical Council](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using oral ketamine outside its authorised indications.

### *Evidence statements*

- One literature review ([Blonk et al. 2010](#)) that has assessed oral ketamine for treating adults with chronic pain was identified. Two small placebo-controlled randomised controlled trials (RCTs), and 1 small case series of n-of-1 trials included in the review (and discussed below) form the evidence base for this summary. In addition, 2 case series ([Cvrcek 2008](#) and [Enarson](#)

[et al. 1999](#)) that were included in the review are also briefly described because they had longer treatment durations and provide more information on safety.

- One small double-blind crossover RCT ([Rabben et al. 1999](#)) found that 5 of 26 adults with trigeminal neuropathic pain had reduced pain on the days after taking oral ketamine at night (ketamine was given for 3 days). Significance testing between oral ketamine and placebo was not reported and all participants had participated in a trial of intramuscular ketamine and midazolam compared with pethidine 1 week before.
- One small crossover RCT ([Furuhashi-Yonaha et al. 2002](#)) in 8 adults with chronic neuropathic pain found that treatment for 1 week with oral ketamine was associated with a statistically significant reduction in mean pain score, but it is not clear if this was compared with baseline pre-ketamine score or with score after placebo. To be enrolled, participants were required to have had pain relief previously with intravenous ketamine.
- One small case series of n-of-1 trials ([Haines and Gaines 1999](#)) included 21 adults with chronic pain that was not adequately controlled on standard therapies. The study consisted of an initial 1-week open-label run-in period with oral ketamine, followed by n-of-1 crossover RCTs (consisting of 3 randomised pairs of 1 week each of oral ketamine and placebo) in 9 people who reported benefit without adverse effects from oral ketamine in the run-in period. The study found that 3 out of 9 people had a greater reduction in pain scores on a visual analogue scale (VAS) after oral ketamine treatment in the n-of-1 RCTs compared with placebo, but this was only statistically significant in 2 of the people.
- Oral ketamine was frequently associated with adverse effects in randomised trials and cases series. Almost half of people withdrew from treatment because of adverse effects within a 1 week run-in with oral ketamine in a case series of n-of-1 trials ([Haines and Gaines 1999](#)). In a case series ([Enarson et al. 1999](#)), 9 out of 21 people withdrew from oral ketamine because of adverse effects, 5 of these in the first 10 days of treatment.
- The most common adverse effects of oral ketamine reported in [Haines and Gaines \(1999\)](#) included headache, light headedness, dizziness, tiredness and a 'nervous floating feeling'. [Furuhashi-Yonaha et al. \(2002\)](#) also reported headache as an adverse effect of oral ketamine, and [Rabben et al. \(1999\)](#) reported 'mental' adverse effects with oral ketamine. In a case series of oral ketamine given for 3 months ([Cvrcek 2008](#)), the most common adverse effects included drowsiness, dizziness, dry mouth and sedation.
- The summary of product characteristics for ketamine hydrochloride solution for injection or infusion ([Ketalar](#), Pfizer) states that the most common adverse effects are hallucination, abnormal dreams or nightmares, confusion, agitation, abnormal behaviour, nystagmus,

hypertonia, tonic clonic movements, diplopia, increased blood pressure, heart rate or respiratory rate, nausea, vomiting, erythema and morbilliform rash.

- A phase I dose-ranging pilot study was identified that assessed oral ketamine for 14 days in 12 young people with chronic pain ([Bredlau et al. 2013](#)). Five young people had improved pain with dosages of between 0.25 and 1.0 mg/kg 3 times daily. When oral ketamine was given within this dose range, adverse effects were reported by most participants, but none were dose limiting. Two people experienced dose-limiting adverse effects at dosages of 1.5 mg/kg 3 times daily.

## Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

## Efficacy

This evidence summary includes 2 RCTs, and 1 case series of n-of-1 trials comparing oral ketamine with placebo in adults with chronic pain (a double-blind crossover trial [[Rabben et al. 1999](#)]; a crossover trial for which blinding was not described [[Furuhashi-Yonaha et al. 2002](#)]; and a case series of n-of-1, crossover trials in which participants were blinded to treatment but it is unclear if investigators were [[Haines and Gaines 1999](#)]). All of the studies had fewer than 30 participants and all assessed pain using a VAS. The dosage of oral ketamine varied in the trials: 4 mg/kg once daily in 1 trial; 0.5 mg/kg every 6 hours in 1 trial; and 20 to 100 mg once daily in 1 trial.

The trial by [Rabben et al. \(1999\)](#) had 2 phases. 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.

In the trial by [Furuhashi-Yonaha et al. \(2002\)](#), participants were randomised to either oral ketamine 0.5 mg/kg or placebo every 6 hours for 1 week and then crossed over to the alternative treatment. Participants were enrolled in the study if they had previously reported a pain benefit with intravenous ketamine. It was stated that oral ketamine was associated with a statistically

significant reduction in mean pain score, but it is not clear what pain score was used, or if the scores compared with baseline pre-ketamine pain scores or with scores after placebo.

In the case series of n-of-1 trials reported by [Haines and Gaines \(1999\)](#), 21 participants had a 1-week run-in with oral ketamine liquid 20 to 100 mg once daily. Nine participants who reported reduced pain without excessive adverse effects during this run-in period were then randomised to either oral ketamine liquid or placebo for 1 week on 3 occasions, followed by crossover to the alternative treatment in an n-of-1 RCT. Three of 9 participants had a greater reduction in pain scores on a VAS after oral ketamine treatment in the n-of-1 RCTs compared with placebo (but this was only statistically significant in 2 people). These 3 people were considered by the study authors to be 'responders' to treatment (not further defined). All 3 participants were taking concomitant opioids, and 1 reported severe adverse effects while receiving oral ketamine and chose not to continue with treatment after the trial.

Details of the RCTs and case series of n-of-1 trials are provided in tables 1, 2 and 3 below.

**Table 1 Summary of [Rabben et al. \(1999\)](#) (adults with trigeminal neuropathic pain)**

	Oral ketamine 4 mg/kg once daily at bedtime	Oral placebo	Analysis
<a href="#">Rabben et al. (1999)</a> : double-blind randomised trial			
Randomised	n=26		
<b>Efficacy</b>			
Outcome: reduced pain on days after treatment was given at bedtime	19.2% (5 of 26)	NR	All 5 participants also reported reduced pain with intramuscular ketamine.
<b>Safety</b>			

Adverse effects	NR	NR	The authors report that the 'mental' adverse effects with oral ketamine were longer lasting and more pronounced than those experienced after intramuscular ketamine and midazolam, but do not describe what the 'mental' adverse effects were.
Abbreviations: n, number of patients; NR, not reported.			

**Table 2 Summary of *Furuhashi-Yonaha et al. (2002)* (adults with chronic neuropathic pain)**

	Oral ketamine 0.5 mg/kg 6-hourly	Oral placebo	Analysis
Furuhashi-Yonaha et al. (2002): crossover trial			
Randomised	n=8		
<b>Efficacy</b>			
Outcome: mean pain score (SD) using VAS	Before: 77.6 (15.5) After: 49.1 (11.4), p<0.05	Before: 78.8 (13.9) After: 67.9 (12.7)	Analysis included all 8 participants. It is unclear what pain score was used, or if the statistically significant reduction in mean pain score after treatment with ketamine was compared with baseline pre-ketamine pain scores or with scores after placebo.
Outcome: mean allodynia (SD) using a 4-point verbal rating scale	Before: 2.5 (0.6) After: 1.5 (0.6)	Before: 2.5 (0.6) After: 2.5 (0.6)	Analysis included 4 of 8 participants
<b>Safety</b>	n=8		

Number of participants reporting adverse effects	3 of 8	NR	
Abbreviations; n, number of patients; NR, not reported; SD, standard deviation, VAS, visual analogue scale.			

**Table 3 Summary of *Haines and Gaines (1999)* (adults with chronic neuropathic pain)**

	Oral ketamine 20 to 100 mg once daily	Oral placebo	Analysis
<u>Haines and Gaines (1999)</u> : randomised crossover n-of-1 trials			
Open-label run-in with oral ketamine	n=21	NA	Only participants reporting a benefit without intolerable adverse effects progressed to randomisation.
Randomised to the n-of-1 trial	n=9		
<b>Efficacy</b>			
Outcome: 'responders'	3 of 9 (33.3%) randomised participants		The authors report that 3 of 9 participants were 'responders' (not further defined) to oral ketamine. One of the participants that was reported to be a 'non-responder' to oral ketamine reported lower pain scores during placebo weeks.
Outcome: 'non-responders'	6 of 9 (66.7%) randomised participants		
<b>Safety</b>			

Participants reporting adverse effects leading to withdrawal during 1-week run-in	10 of 21 (47.6%)	NA	Overall, 17 of 21 participants recorded adverse effects during the run-in and n-of-1 trials. It is unclear to which group participants were assigned when they experienced these adverse effects. The most commonly reported adverse effects were light headedness, dizziness, tiredness, headache and a 'nervous floating feeling'.
Adverse effects during n-of-1 trial	NR	NR	
Abbreviations: n, number of patients; NA, not applicable; NR, not reported.			

Two case series assessing oral ketamine, with follow up periods of 3 months and more than 1 year, have also been described. See the [evidence review: efficacy](#) section for more details.

No RCTs were identified assessing oral ketamine in children or young people with chronic pain. One phase I pilot study ([Bredlau et al. 2013](#)) examined the efficacy and safety of oral ketamine for 14 days in a dose-ranging study in 12 young people with chronic pain. Ketamine solution for injection was used orally. Five young people reported improved pain on a numerical rating scale with dosages of between 0.25 and 1.0 mg/kg 3 times daily, and no dose-limiting toxicities occurred in people receiving doses within this range.

## Safety

### *Product characteristics*

The summary of product characteristics for ketamine hydrochloride solution for injection or infusion ([Ketalar](#); licensed for use by intravenous or intramuscular injection, or intravenous infusion as an anaesthetic agent for diagnostic and surgical procedures in children, young people and adults) states that the most common adverse drug reactions (reported to affect between 1 and 10 people in every 100 receiving the drug) are hallucination, abnormal dreams or nightmares, confusion, agitation, abnormal behaviour, nystagmus, hypertonia, tonic clonic movements, diplopia, increased blood pressure, heart rate or respiratory rate, nausea, vomiting, erythema and morbilliform rash. Cases of cystitis, including haemorrhagic cystitis, have been reported in people being given

ketamine on a long-term basis; therefore the summary of product characteristics states that 'ketamine is not indicated nor recommended for long-term use'.

The summary of product characteristics states that Ketalar has been reported as being a drug of abuse, with reports suggesting that ketamine produces a variety of symptoms, including flashbacks, hallucinations, dysphoria, anxiety, insomnia and disorientation. It states that if the drug is used on a daily basis for a few weeks, dependence and tolerance may develop, particularly in people with a history of drug abuse and dependence.

### ***Randomised trials and case series in adults***

In the trial by Rabben et al. (1999), limited detail is provided about adverse effects.

In the study by Furuhashi-Yonaha et al. (2002), 2 of 8 participants reported headache after 1 week of treatment with oral ketamine. The study authors report that this was relieved with loxoprofen. One participant reported nightmares (reduced by the co-administration of diazepam) and slight dizziness (no treatment needed).

In the case series of n-of-1 trials by Haines and Gaines (1999), more than half of the participants discontinued treatment during an initial 1-week open-label run-in with oral ketamine because of lack of benefit and / or intolerable adverse effects (12 of 21 people). Adverse effects were recorded in 17 of 21 participants. The most common were light headedness (4 people), dizziness (4 people), tiredness (4 people), headache (3 people) and a 'nervous floating feeling' (3 people), and 1 person reported bad dreams.

In the case series by Cvrcek (2008), 4 of 32 participants (12.5%) withdrew during 3 months of treatment with oral ketamine because of adverse effects. Five other participants withdrew because of reported treatment failure (15.6%). The most common adverse effects with oral ketamine, affecting more than 15% of participants, were drowsiness (25.0%, 8 people), dizziness (22.0%, 7 people), dry mouth (18.8%, 6 people) and sedation (18.8%, 6 people). It is not reported which adverse effects caused participants to withdraw from treatment.

In the case series by Enarson et al. (1999), 9 of 21 participants (42.9%) withdrew because of adverse effects, of which 5 (23.8%) discontinued therapy within the first 10 days of treatment. The most common adverse effects causing withdrawal were psychomimetic symptoms described as 'elevator effect' and dissociative feelings (figures not reported). Other common adverse effects causing withdrawals from treatment were alertness disturbances (somnolence or insomnia) and sensory changes (taste changes, numbness, tingling, feeling hot or cold).

### ***Phase I pilot study in children and young people***

In the phase I pilot study in 12 young people by [Bredlau et al. \(2013\)](#), all but 1 participant reported at least 1 adverse effect with oral ketamine. However, no participants experienced dose-limiting toxicities with 0.25, 0.5 or 1.0 mg/kg per dose oral ketamine. Two out of 3 participants experienced dose-limiting toxicities (anorexia and depressed levels of consciousness) while receiving 1.5 mg/kg per dose oral ketamine. One of these participants also experienced dysuria and discontinued treatment because of concerns about these symptoms possibly preceding haemorrhagic cystitis. Delayed dysphoria (examples described were confusion and dizziness) was experienced by 7 of 12 participants (58.3%). The study authors report that many of the participants experienced fatigue or somnolence after their first oral ketamine dose, but this resolved within 1 to 2 hours.

### **Cost effectiveness and cost**

No studies on the cost effectiveness of oral ketamine for treating chronic pain were identified.

Data in the [current drug usage](#) section suggests that between November 2012 and October 2013, approximately 80% of dispensed prescription items for all ketamine preparations prescribed in primary care in England was for ketamine oral liquid formulations, whereas approximately 20% was for injection formulations. It is not known for which indications ketamine was being prescribed, or how much, if any, prescribing of the solution intended for injection was for off-label oral use.

The [NHS Electronic Drug Tariff \(January 2014\)](#) lists the following prices for ketamine oral solution or suspension in Part VIII B, Arrangements for payment for specials and imported unlicensed medicines:

- Ketamine 50 mg/5 ml oral solution: £215.90 for minimum volume of 200 ml plus £0.01 for each extra ml.
- Ketamine 50 mg/5 ml oral suspension: £132.25 for minimum volume of 200 ml plus £0.01 for each extra ml.

No price is listed for other strengths of liquid formulation, and the cost of these will differ depending on the source.

[MIMS \(January 2014\)](#) lists the following costs for Ketalar:

- 10 mg/ml, 1×20 ml vial=£5.06.
- 50 mg/ml, 1×10 ml vial=£8.77.

- 100 mg/ml, 1×10 ml vial=£16.10.

## Relevance to NICE guidance programmes

This use of oral ketamine for chronic pain is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued the following clinical guidelines related to chronic pain:

- [Osteoarthritis](#) (NICE clinical guideline 177)
- [Neuropathic pain – pharmacological management](#) (NICE clinical guideline 173)
- [Low back pain](#) (NICE clinical guideline 88)
- [Rheumatoid arthritis](#) (NICE clinical guideline 79)
- [Multiple sclerosis](#) (NICE clinical guideline 8)

NICE has issued the following interventional procedure guidance related to chronic pain:

- [Peripheral nerve-field stimulation for chronic low back pain](#) (NICE interventional procedure guidance 451)
- [Percutaneous electrical nerve stimulation for refractory neuropathic pain](#) (NICE interventional procedure guidance 450)
- [Deep brain stimulation for refractory chronic pain syndromes \(excluding headache\)](#) (NICE interventional procedure guidance 382)
- [Non-rigid stabilisation techniques for the treatment of low back pain](#) (NICE interventional procedure guidance 366)
- [Laparoscopic uterine nerve ablation \(LUNA\) for chronic pelvic pain](#) (NICE interventional procedure guidance 234)
- [Percutaneous disc decompression using coblation for lower back pain](#) (NICE interventional procedure guidance 173)
- [Percutaneous intradiscal radiofrequency thermocoagulation for lower back pain](#) (NICE interventional procedure guidance 83)

NICE has issued the following technology appraisal guidance related to chronic pain:

- [Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin](#) (NICE technology appraisal guidance 159)

NICE has also issued guidance that includes recommendations for the licensed indication for ketamine:

- [Sedation in children and young people](#) (NICE clinical guideline 112).

## Intervention and alternatives

Ketamine induces sedation, immobility, amnesia and marked analgesia. Its mechanism of action is thought to include binding to N-methyl-D-aspartate (NMDA) receptors in the central nervous system, interactions with central and spinal opioid receptors, and interactions with norepinephrine, serotonin and muscarinic cholinergic receptors. Activity on NMDA receptors may be responsible for the analgesic as well as the psychiatric effects of ketamine (see the [Ketalar summary of product characteristics](#)).

Ketamine hydrochloride solution for injection or infusion ([Ketalar](#), Pfizer) is licensed in the UK as an anaesthetic agent for diagnostic and surgical procedures in children, young people and adults.

Oral liquid preparations of ketamine are not licensed in the UK, so use of these preparations which are prepared by 'specials' manufacturers, is unlicensed. When ketamine solution for injection or infusion is used orally, this is off-label use.

## Condition

According to [Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin](#) (NICE technology appraisal guidance 159), chronic pain can be defined as pain that persists for more than several months, or beyond the normal course of a disease or expected time of healing. It can affect people of all ages and, in general, its prevalence increases with age. The [British Pain Society](#) defines chronic pain as continuous, long-term pain of more than 12 weeks or after the time that healing would have been thought to have occurred in pain after trauma or surgery.

Chronic pain is accompanied by physiological and psychological changes, such as sleep disturbances, irritability, medication dependence and frequent absence from work. Emotional withdrawal and depression are also commonly associated with chronic pain (see the NICE technology appraisal guidance on [spinal cord stimulation for chronic pain](#)).

NICE's technology appraisal guidance on [spinal cord stimulation for chronic pain](#) estimates that prevalence of chronic pain in the UK varies from less than 10% to more than 30%, depending on the specific definition of chronic pain used.

Neuropathic pain is a type of pain that can be peripheral or central in origin and is caused by nervous system damage or dysfunction that can become chronic. According to [Neuropathic pain – pharmacological management](#) (NICE clinical guideline 173), a review of the epidemiology of chronic pain found that there is still no accurate estimate available for the population prevalence of neuropathic pain.

Examples of conditions that can cause central neuropathic pain include stroke, spinal cord injury and multiple sclerosis. Examples of conditions that have peripheral neuropathic pain as a symptom are painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, radicular pain, post-surgical chronic neuropathic pain and neuropathic cancer pain (see the [NICE clinical guideline on pharmacological management of neuropathic pain](#)).

### *Alternative treatment options*

According to the NICE technology appraisal guidance on [spinal cord stimulation for chronic pain](#), the goal of treatment for chronic pain is to make pain tolerable and to improve functionality and quality of life. Non-pharmacological interventions may be used, including physiotherapy, acupuncture, transcutaneous electrical nerve stimulation (TENS) and psychological therapies. Pharmacological interventions may include non-steroidal anti-inflammatory drugs (NSAIDs), tricyclic and other antidepressants, anticonvulsants, analgesics and opioids. There may also be surgical options for some chronic pain conditions.

Despite management with pharmacological and non-pharmacological interventions, complete pain relief is rarely achieved for people with chronic pain (see the NICE technology appraisal guidance on [spinal cord stimulation for chronic pain](#)).

NICE clinical guideline on [pharmacological management of neuropathic pain](#) recommends amitriptyline (off-label use), duloxetine (licensed use for diabetic peripheral neuropathic pain), gabapentin (licensed use for peripheral neuropathic pain) or pregabalin as first-line pharmacological treatment for people with neuropathic pain (excluding trigeminal neuralgia). If the initial treatment is not effective or is not tolerated, one of the remaining 3 drugs should be offered, and consideration should be given to switching again if the second and third drugs tried are also not effective or not tolerated. Carbamazepine is recommended as initial treatment for people with trigeminal neuralgia.

NICE has issued interventional procedure guidance on a number of non-pharmacological interventions related to chronic pain and these are listed in the [Relevance to NICE guidance](#) section.

## Evidence review: efficacy

### *Adults with chronic pain*

One literature review was identified ([Blonk et al. 2010](#)) that included studies evaluating the efficacy of ketamine used orally as an analgesic for chronic pain in adults, with no restriction on the type of studies included.

The review included 2 randomised controlled trials (RCTs), and 1 case series of n-of-1 trials that compared oral ketamine with placebo ([Rabben et al. 1999](#), [Furuhashi-Yonaha et al. 2002](#) and [Haines and Gaines 1999](#)), which are summarised below. Details of the [Furuhashi-Yonaha et al. \(2002\)](#) trial are only available from a published letter.

One other RCT included in the [Blonk et al. \(2010\)](#) review assessed oral ketamine as add-on therapy to morphine ([Lauretti et al. 1999](#)). This RCT was in people with chronic cancer pain, a population that is outside of the scope of this evidence summary and has not been further described.

Two case series ([Cvrcek 2008](#) and [Enarson et al. 1999](#)) that were included in the review by [Blonk et al. \(2010\)](#) are also briefly described below because they had longer treatment durations and provide more information on safety.

None of the studies included in the review by [Blonk et al. \(2010\)](#) were of high methodological quality as assessed by those authors.

The review concludes that use of oral ketamine for treating chronic pain in adults is not supported because of the lack of efficacy data and poor safety profile, but that oral ketamine as add-on therapy may have a limited place in the treatment of complex chronic pain if other therapeutic options have failed.

There are no published RCTs on the long-term psychological effects of taking oral ketamine.

## Rabben et al. (1999)

Rabben et al. (1999) performed a double-blind, placebo-controlled crossover RCT of oral ketamine that included 26 adults with trigeminal neuropathic pain (also classified as secondary trigeminal neuralgia) who had constant orofacial pain. Most of the participants related their pain to dental procedures causing nerve damage such as endodontic treatment, apical surgery or extractions. All participants had unilateral pain with somatosensory disturbances such as allodynia, dysesthesia and hypoesthesia, and most had been treated with drugs and procedures without or with minimal temporary effect. People with temporomandibular joint syndrome, muscular pain, a psychiatric diagnosis or pain on a visual analogue scale (VAS) of below 25 were excluded. The mean pain duration of participants was 6 years (range 6 months to 20 years).

Thirty participants (13.3% male, mean age 57.6 years, age range 29 to 89 years) were initially randomised to receive either a single dose of intramuscular ketamine combined with midazolam or intramuscular pethidine, and crossed over to the alternative treatment 1 week later. Four participants withdrew from the trial because of pethidine-related nausea or causes unrelated to the treatment. After 1 week, 26 participants who completed the intramuscular ketamine trial were randomised to either a single dose of oral ketamine (4 mg/kg) or placebo given for 3 consecutive days at bedtime to see if pain was reduced the following day, and then crossed over to the alternative treatment. Limited detail is provided about the crossover and it is not clear if there was a wash-out period between treatments. Capsules used for oral ketamine and placebo were identical in design.

Primary and secondary outcomes of the study were not described. For ketamine given orally, pain was assessed using a VAS ranging from a score of 0 (no pain) to a score of 100 (intolerable pain). Assessments were made in the morning and at bedtime for 3 days before, during and after the doses.

Limited results of the trial assessing oral ketamine are described by the study authors, so the effect of oral ketamine on pain compared with placebo is difficult to assess.

Five of 26 participants (19.2%) experienced pain relief on the days after oral ketamine was given at night, all of whom reported reduced pain after ketamine was given intramuscularly in the first part of the study. Significance testing between oral ketamine and placebo was not reported for this finding. Other reported results were:

- Six participants who did not report reduced pain with intramuscular ketamine also reported no statistically significant reduction in mean pain scores after oral ketamine compared with placebo.
- Seven participants reported to have a long-lasting analgesic effect (not further defined) after intramuscular ketamine had statistically significant reductions in mean pain scores on day 2 and 3 of oral ketamine administration compared with placebo ( $p < 0.05$  for both days).
- Six participants reported to have a short-lasting analgesic effect (not further defined) after intramuscular ketamine did not have statistically significant differences in mean pain levels after oral ketamine compared with placebo.

Adverse effects reported by [Rabben et al. \(1999\)](#) are described in the [Safety](#) section.

### **Furuhashi-Yonaha et al. (2002)**

[Furuhashi-Yonaha et al. \(2002\)](#) performed a placebo-controlled crossover RCT of oral ketamine that included 8 people (62.5% male, mean age 53.3 years) with chronic neuropathic pain, all of whom had pain relieved with intravenous ketamine before enrolment into this trial (no further detail is provided). Four participants had complex regional pain syndrome, 2 had visceral pain, 1 had phantom limb pain and 1 had postherpetic neuralgia. The mean duration of pain in participants was approximately 4.5 years.

Participants were randomly assigned to either 0.5 mg/kg oral ketamine syrup or the same volume of placebo syrup every 6 hours for 1 week. The crossover aspect of the trial is not described and it is unclear if there was a wash-out period before crossover to the alternative treatment. It is not clear if any blinding to treatment was in place. Assessments were made for pain (using a VAS; range not described but assumed to have been 1 to 100, with higher scores indicating more severe pain based on scores provided) and allodynia (using a 4-point verbal rating scale) before treatment and at the end of each week of treatment.

Oral ketamine was associated with a statistically significant reduction in mean pain score ( $p < 0.05$ ), but it is not clear if this was compared with baseline pre-ketamine pain scores or with scores after placebo. After 1 week of treatment, the mean pain score was 49.1 with oral ketamine (77.6 before treatment) compared with 67.9 with placebo (78.8 before treatment). There was a non-significant reduction in allodynia after oral ketamine compared with placebo. Reductions in pain and allodynia were reported to have lasted 6 to 8 hours, but it is not clear when or how these additional assessments were performed.

Four participants were reported to have continued taking oral ketamine after the trial (treatment duration range 9 to 54 months) and had ongoing assessments for pain and adverse effects. The authors report that severity of pain during daily life was reduced in all 4 participants but no further detail was provided.

## Haines and Gaines (1999)

Haines and Gaines (1999) performed single-blind, placebo-controlled, n-of-1 crossover trials in adults with chronic neuropathic pain not satisfactorily controlled on standard therapies who were recruited from a pain management clinic.

Of 21 participants entered into the study (52.4% male), 7 had a diagnosis of neuropathic back pain, 5 had post herpetic neuralgia, 2 had pain after stroke and 2 had pain after spinal cord surgery. The remaining participants had post-traumatic neuralgia, cervical myelopathy, phantom pain, multiple sclerosis or burning feet syndrome. The mean duration of prior pain was approximately 10 years (range 1 to 30 years).

Participants completed a daily pain diary for 1 week, followed by a 1-week initial open-label run-in with oral ketamine. The starting dose during the run-in period was 20 mg oral ketamine once daily, after which blood pressure, pulse and respiration were monitored and participants were observed for adverse effects. The dose of oral ketamine could be increased by 10 mg each day until an analgesic effect was noticed, adverse effects occurred or a maximum dose of 100 mg was reached. The study authors report that this run-in allowed the optimal dose for each participant to be determined, which was used for participants included in the n-of-1 RCTs.

Only participants who reported reduced pain without excessive adverse effects in the run-in period (9 participants) were then randomised to either oral ketamine or placebo for 1 week on 3 occasions followed by crossover to the alternative treatment (that is, 6 weeks of treatment in total: 3 weeks with oral ketamine and 3 weeks with placebo). Ketamine and placebo liquid preparations were flavoured to be similar in taste so that participants could be blinded to treatment allocation. There was no wash-out period between crossover, and the authors report deciding that once-daily oral ketamine would allow adequate time for wash-out between treatments. Participants continued their usual pain treatments (pharmacological and non-pharmacological) for the duration of the study (run-in and n-of-1 trial).

Primary and secondary outcomes of the study were not described. Pain was assessed using a daily pain diary that included 2 VASs for recording the intensities of up to 2 pain qualities (for example, aching pain or burning pain) ranging from 'no pain' to 'most severe pain imaginable'. Participants

were also asked to record answers to 2 questions about pain and mood using a 7-point Likert scale. The pain diary was completed daily during the run-in period 1 hour after taking ketamine; it is not reported when pain was recorded during the placebo-controlled part of the study. VAS, pain and mood scores are reported to have been converted into graphical form but these were not shown.

Of 21 participants, 12 (57.1%) did not progress to randomisation in the n-of-1 trials after the 1 week run-in with oral ketamine; 10 of the 12 participants experienced adverse effects that the authors report prevented the dose of ketamine being increased.

All 9 participants who progressed to the n-of-1 trial part of the study completed the weekly treatment cycles. Three participants had reduced pain scores and were considered by the study authors to be 'responders' (not further defined) to oral ketamine. These 'responders' were all taking more concomitant opioid drugs than the 6 'non-responders'. Of the 3 'responders', 1 had a statistically significant lower pain score on the VAS after oral ketamine compared with placebo, but pain relief was reported to only last 1 to 2 hours and was accompanied by severe adverse effects. This person did not continue taking oral ketamine after the trial. Two other 'responders' had a greater reduction in pain scores on the VAS after oral ketamine compared with placebo; this was statistically significant in 1 case ( $p < 0.05$ ) but not in the other ( $p < 0.15$ ). Both participants continued to take oral ketamine after the trial, but 1 stopped treatment at 3 months because of worsening pain and no perceived benefit. The other participant remained on ketamine 40 mg daily after completing the trial.

The remaining 6 participants were reported to be 'non-responders' to oral ketamine, including 1 participant who had a statistically significant greater reduction in pain scores with placebo compared with ketamine ( $p < 0.005$ ).

Three of the participants considered to be 'non-responders' were reported to be able to distinguish ketamine from placebo because of the adverse effects. Adverse effects reported by [Haines and Gaines \(1999\)](#) are described in the [Safety](#) section.

## Case series

Two case series that met the inclusion criteria for this evidence summary and were included in the literature review by [Blonk et al. \(2010\)](#) are briefly described below because they had longer treatment durations than the RCTs described above; without a comparator they provide limited information on efficacy, but do provide some additional information on tolerability and adverse effects.

Cvrcek (2008) was a case series that assessed use of oral ketamine in 32 adults (34.4% male) with diabetic polyneuropathy and postherpetic neuralgia whose pain had not responded to pharmacological therapy. Participants initially received a single ketamine infusion followed by 30 mg of oral ketamine (given in 6 ml of saline) 5 times daily for 3 months.

During 3 months of treatment, 5 people (15.6%) withdrew because of reported treatment failure and 4 people (12.5%) withdrew because of adverse effects. There was a statistically significant reduction in pain intensity (assessed using a 10-point VAS, with higher scores indicating more severe pain) after 1 week of treatment with oral ketamine (median pain score of 3.9) compared with pain intensity before treatment (median pain score of 6.6;  $p=0.002$ ). The median score for pain intensity was lower after 3 months of treatment, but this was only displayed graphically with no data or statistical analyses.

Enarson et al. (1999) was a retrospective case series assessing oral ketamine in addition to ongoing therapies in 21 adults (age range 29 to 81 years, 38.1% male) with chronic neuropathic pain that had not responded to analgesic therapies. Ketamine was given at a starting dose of 100 mg/day (or 40 mg/day for people who were described as being hypersensitive to medications) in divided doses, titrated by 40 mg/day every 2 days until treatment effect or adverse effects occurred. Final doses ranged from 40 to 500 mg/day (median dose 220 mg/day).

Nine participants (42.9%) withdrew from treatment because of adverse effects, of whom 5 (23.8%) discontinued therapy within the first 10 days of treatment. Seven participants (33.3%) were reported to have reduced pain (not further defined) with oral ketamine, but 4 of these people withdrew from treatment because of adverse effects. The study authors report that 3 participants had reduced pain and reduced analgesic use with oral ketamine treatment (dose range 100 to 240 mg/day) for over 1 year.

### *Young people with chronic pain*

Bredlau et al. (2013) reported a dose-ranging phase I pilot study (case series) in 12 young people (25% male) aged 11 to 19 years (mean age 16 years) with chronic pain that had lasted longer than 3 months. The aim of the trial was to identify the maximum tolerated dose of oral ketamine. Pain diagnoses included headache (2 people), joint pain (2 people), bone pain, chronic pancreatitis, Crohn's disease, scoliosis, spina bifida, hypermobility, oesophageal spasm and amplified musculoskeletal pain syndrome. All participants had previously received treatment with 2 or more non-opioids.

Participants were given oral ketamine 3 times daily for 12 consecutive days followed by 2 days at 50% of their original dose to minimise withdrawal. Doses ranged from 0.25 to 1.5 mg/kg per dose and were given at increasing doses dependent on dose-limiting toxicities. Oral ketamine was taken as a liquid, which was prepared using ketamine solution for injection that was diluted in sterile water to a concentration of 10 mg/ml and added to between 0.5 and 1 ounces of soda or orange juice (based on participant preference). Participants were instructed to continue their current pain therapies during treatment with oral ketamine.

Three participants appear to have not completed the 14-day treatment period; 2 because of a dose-limiting toxicity while receiving oral ketamine at 1.5 mg/kg per dose. Pain score was assessed using a numerical rating scale (NRS) on day 1, day 7 and day 14 (participants had to have an NRS score of more than 4 out of 10 to be included, with higher scores indicating more severe pain). Participants were asked to report their pain at the exact time of assessment only, and this single assessment may have not accurately reflected their average pain scores. Participants were contacted twice weekly and asked to report any adverse effects.

After 14 days of oral ketamine, 5 of 12 participants (41.7%) reported improved pain scores: 2 young people had complete resolution of pain and 3 had a pain reduction of 2 or more points on the NRS (out of 10). These participants were receiving doses of 0.25 or 1.0 mg/kg oral ketamine. The study authors report that of the 5 young people with improved pain, 3 reported improved pain control that was sustained for up to 4 weeks after discontinuation of oral ketamine. One young person experienced increased pain while on ketamine at 0.5 mg/kg per dose. This person originally had a diagnosis of headache and joint pain and was later diagnosed with a somatisation syndrome and complex regional pain syndrome. The remaining 6 participants had no change in pain scores after treatment with oral ketamine. Adverse effects reported by [Bredlau et al. \(2013\)](#) are described in the [Safety](#) section.

A maximum tolerated dose of oral ketamine for young people was not estimated because of the small number of participants included in the study. The authors concluded that oral ketamine at a dosage of 0.25 to 1.0 mg/kg 3 times daily appears to be safe when taken by young people with chronic pain for 2 weeks. However, the small number of included participants and the lack of a control arm limit the conclusions that can be drawn.

According to [ClinicalTrials.gov](#), a dose-ranging phase II RCT of oral ketamine for treating chronic pain in children and young people (age range 8 to 20 years) ([Ketamine in Chronic Kid's Pain \[KiCK Pain\]](#)) is recruiting participants and has an estimated completion date of May 2017.

## Evidence review: safety

The summary of product characteristics for ketamine hydrochloride solution for injection or infusion ([Ketalar](#); licensed for use by intravenous or intramuscular injection, or intravenous infusion as an anaesthetic agent for diagnostic and surgical procedures) states that the most common adverse drug reactions (reported to affect between 1 and 10 people in every 100 receiving the drug) are hallucination, abnormal dreams or nightmares, confusion, agitation, abnormal behaviour, nystagmus, hypertonia, tonic clonic movements, diplopia, increased blood pressure, heart rate or respiratory rate, nausea, vomiting, erythema and morbilliform rash. Cases of cystitis, including haemorrhagic cystitis, have been reported in people being given ketamine on a long-term basis; therefore the summary of product characteristics states that 'ketamine is not indicated nor recommended for long term use'.

The summary of product characteristics states that [Ketalar](#) has been reported as being a drug of abuse, with reports suggesting that ketamine produces a variety of symptoms, including flashbacks, hallucinations, dysphoria, anxiety, insomnia and disorientation. It states that if the drug is used on a daily basis for a few weeks, dependence and tolerance may develop, particularly in people with a history of drug abuse and dependence.

In 2012 the Advisory Council on the Misuse of Drugs reviewed the misuse and harms of ketamine and in December 2013 it [recommended](#) that ketamine be upgraded to a class B and, subject to the outcome of a public consultation, a Schedule 2 drug, following increased evidence of bladder damage from frequent misuse (see [regulatory status of oral ketamine](#)).

On 10 June 2014, the Parliamentary Order reclassifying ketamine as a class B drug came into force. Ketamine is not being rescheduled immediately. In line with the Advisory Council on the Misuse of Drugs' (ACMD) advice, the Home Office will carry out a public consultation later this year to assess the impact of rescheduling ketamine to Schedule 2. A final decision on the appropriate schedule for ketamine will be made after the consultation. Until then ketamine will remain a Schedule 4 Part 1 drug (see the [Medicines and Healthcare Products Regulatory Agency Medicines regulatory news on the control of lisdexamphetamine, tramadol, zaleplon, zopiclone and reclassification of ketamine](#) for more information).

### *Adults with chronic pain*

In the trial by [Rabben et al. \(1999\)](#), adverse effects were mostly reported for the initial treatment with intramuscular ketamine, and limited detail is provided about adverse effects after oral ketamine. The study authors report that 'mental' adverse effects after oral ketamine were

qualitatively similar but lasted longer and were more pronounced than adverse effects after intramuscular ketamine and midazolam. Dizziness, sedation, blurred vision, xerostomia and a feeling of insobriety were all reported in more than 60% of people receiving intramuscular ketamine in addition to midazolam, but it is not described which of these adverse effects were considered to be mental adverse effects. The study authors also state that adverse effects were reported only by participants who did not fall asleep in the 20 to 30 minutes after taking oral ketamine.

Four participants with pain relief after oral ketamine were reported to have mental adverse effects, which were reported to be disturbing in 2 people. No further safety data were provided for the use of oral ketamine.

In the trial by [Furuhashi-Yonaha et al. \(2002\)](#), 2 of 8 participants reported headache after 1 week of treatment with oral ketamine. The study authors report that this was relieved with loxoprofen. One participant reported nightmares (reduced by the co-administration of diazepam) and slight dizziness (no treatment needed). No adverse effects were reported by 4 participants who continued treatment with oral ketamine in an open-label phase of the study for between 9 and 54 months after the trial.

In the study by [Haines and Gaines \(1999\)](#), almost half of the participants discontinued treatment during an initial 1-week open-label run-in with oral ketamine because of adverse effects (10 of 21 people). Two other people withdrew during the 1-week run-in with oral ketamine, but reasons for discontinuation are not described. Adverse effects were recorded by 17 of 21 participants. The most common were light headedness (4 people), dizziness (4 people), tiredness (4 people), headache (3 people) and a 'nervous floating feeling' (3 people), and 1 person reported bad dreams. One of the adults reporting a reduced pain score was reported to have severe adverse effects that prevented him from continuing with oral ketamine after the trial.

In the case series by [Cvrcek \(2008\)](#), 4 of 32 participants (12.5%) withdrew during 3 months of treatment with oral ketamine because of adverse effects. Five other participants withdrew because of reported treatment failure (15.6%). The most common adverse effects with oral ketamine were drowsiness (25.0%, 8 people), dizziness (22.0%, 7 people), dry mouth (18.8%, 6 people) and sedation (18.8%, 6 people). Other reported adverse effects were nausea and vomiting (3 people, 2 of whom were receiving concomitant treatment with dihydrocodeine), memory deterioration (3 people), euphoria (2 people) and a feeling of drunkenness (1 person). It is not reported which adverse effects caused participants to withdraw from treatment.

In the case series by [Enarson et al. \(1999\)](#), 9 of 21 participants (42.9%) withdrew because of adverse effects, of whom 5 (23.8%) discontinued therapy within the first 10 days of treatment. The most common adverse effects causing withdrawal were psychomimetic symptoms described as 'elevator effect' and dissociative feelings (figures not reported). Other common adverse effects causing withdrawals from treatment were alertness disturbances (somnolence or insomnia) and sensory changes (taste changes, numbness, tingling, feeling hot or cold).

### *Young people with chronic pain*

In the phase I pilot study by [Bredlau et al. \(2013\)](#) including 12 young people with chronic pain, the primary safety outcome was the occurrence of a dose-limiting toxicity (graded according to the National Cancer Institute Common Terminology for Adverse Events version 4.0). Any adverse effect with a grade of 3 or higher was considered a dose-limiting toxicity, as were particular grade 2 adverse effects including, but not limited to, hallucinations, delirium, dizziness and hypertension.

All but 1 participant reported at least 1 adverse effect with oral ketamine. However, no participants experienced a dose-limiting toxicity on oral ketamine at 0.25, 0.5 or 1.0 mg/kg per dose. Two of 12 participants (16.7%) experienced a dose-limiting toxicity that was either grade 2 anorexia or grade 2 depressed level of consciousness (also referred to as sedation). These 2 participants were both receiving 1.5 mg/kg per dose of oral ketamine. One of these participants also experienced grade 2 dysuria and, although this resolved within 2 days of treatment discontinuation, the authors report that this was concerning because of a possibility of dysuria preceding haemorrhagic cystitis. Delayed dysphoria (examples described were confusion and dizziness) was experienced by 7 of 12 participants (58.3%). The study authors report that many of the participants experienced fatigue or somnolence after their first oral ketamine dose, but this resolved within 1 to 2 hours.

Three participants appear not to have completed the 14-day treatment period, 2 because of a dose-limiting toxicity while receiving oral ketamine at 1.5 mg/kg per dose.

## **Evidence review: economic issues**

### *Cost effectiveness*

No studies on the cost effectiveness of oral ketamine for treating chronic pain were identified.

## Cost

Data in the [current drug usage](#) section suggest that between November 2012 and October 2013, approximately 80% of dispensed prescription items for all ketamine preparations prescribed in primary care in England was for ketamine oral liquid formulations, whereas approximately 20% was for injection formulations. It is not known for which indications ketamine was being prescribed, or how much, if any, prescribing of the solution intended for injection was for off-label use orally.

The [NHS Electronic Drug Tariff \(January 2014\)](#) lists the following prices for ketamine oral solution or suspension in Part VIIIB, Arrangements for payment for specials and imported unlicensed medicines:

- Ketamine 50 mg/5 ml oral solution: £215.90 for minimum volume of 200 ml plus £0.01 for each extra ml.
- Ketamine 50 mg/5 ml oral suspension: £132.25 for minimum volume of 200 ml plus £0.01 for each extra ml.

No price is listed for other strengths of liquid formulation, and the cost of these will differ depending on the source.

[MIMS \(January 2014\)](#) lists the following costs for Ketalar:

- 10 mg/ml, 1×20 ml vial=£5.06.
- 50 mg/ml, 1×10 ml vial=£8.77.
- 100 mg/ml, 1×10 ml vial=£16.10.

## Current drug usage

Prescription cost analysis reports the following data for dispensed prescriptions for ketamine preparations prescribed in primary care in England between November 2012 and October 2013 inclusive (NHS Business Services Authority: personal communication January 2014):

- Any strength or formulation of ketamine liquid including liquid special, oral solution or oral suspension: 2273 items at a net cost of £521,656.
- Any strength or formulation of ketamine injection (Ketalar or ketamine injection): 529 items at a net cost of £34,817.

It is not known for which indications ketamine was being prescribed, or how much, if any, prescribing of the solution intended for injection was for off-label use orally.

## Evidence strengths and limitations

Two randomised controlled trials (RCTs), and 1 case series of n-of-1 trials evaluating the efficacy of oral ketamine compared with placebo for treating chronic pain in adults that were included in a 2010 literature review ([Blonk et al. 2010](#)) were identified as relevant. The studies all contained small numbers of participants (n=26, n=8, n=21) and were short-term (ranging from 3 days to 6 weeks). Only the trial by [Rabben et al. \(1999\)](#) was described as being double-blind. [Haines and Gaines \(1999\)](#) report that participants were blinded to treatment in the n-of-1 trials, but do not report if investigators were, and [Furuhashi-Yonaha et al. \(2002\)](#) do not report if participants or investigators were blinded to treatment. In addition, none of the studies described whether allocation to treatment was concealed. Lack of blinding and allocation concealment is a potential source of bias.

The dosage of oral ketamine varied between the studies and so it is difficult to reach any conclusions about the optimal dosage for treating chronic pain.

All of the studies used a visual analogue scale to record pain, but none included functional assessments, so it is unclear if reported reductions in pain had an effect on functional ability.

Overall, the studies provide no good quality evidence that oral ketamine improves pain for adults with chronic pain. These studies assessed only the short-term use of oral ketamine, so the longer-term efficacy and safety of oral ketamine in adults cannot be determined.

Two case series (1 prospective, 1 retrospective) were identified that had similar participant numbers to the studies described above, but longer treatment durations (3 months [[Cvrcek 2008](#)] and more than 1 year [[Enarson et al. 1999](#)]). However, the observational nature of these studies and the lack of a control arm limit the interpretations that can be made about efficacy.

No RCTs were identified in children or young people. A phase I pilot study by [Bredlau et al. \(2013\)](#) examined the efficacy and safety of oral ketamine for 14 days in a dose-ranging study in 12 young people with chronic pain. The lack of a control arm, small number of participants and short treatment duration limit the conclusions that can be drawn about the efficacy and safety of oral ketamine for treating chronic pain in young people. The participants in this study were aged 11 to 19 years, so the study does not provide any information on the efficacy and safety of oral ketamine for treating chronic pain in children aged less than 11 years.

## Summary for patients

A [summary written for patients](#) is available on the NICE website.

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## Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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## *Declarations of interest*

Dr Thomas E. Smith has received speaker fees and / or research grants from the following companies in the last 12 months:

- Astellas
- Nevro
- Pfizer
- Allergan
- Medtronic
- Grunenthal

Mr R Andrew Moore has received speaker fees and / or research grants from the following companies in the last 12 months:

- Menarini
- Grunenthal
- Reckitt Benckiser
- MSD
- Novartis

## Appendix: Search strategy and evidence selection

### *Search strategy*

#### General background, guidelines and technology assessments:

##### Broad internet search:

##### Google:

allintitle:ketamine pain oral filetype:pdf

##### Google scholar:

Ketamine pain oral

##### Trip Database:

Ketamine pain oral: all words, anywhere in document, proximity

or Oral ketamine: exact phrase, anywhere in document

or Ketamine in title, chronic pain: exact phrase anywhere in document

### **MEDLINE (via Ovid)**

In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

#### Search Strategy:

1 Ketamine/ (9376)

2 ketamine.ti,ab. (12563)

3 ketalar.ti,ab. (201)

4 1 or 2 or 3 (14044)

5 exp Administration, Oral/ (120283)

6 oral.ti,ab. (430676)

7 5 or 6 (477863)

8 Chronic Pain/ (2715)

9 neuropathic pain.mp. (11784)

10 exp Complex Regional Pain Syndromes/ (4368)

11 (chronic adj pain).ti,ab. (20977)

12 (cancer adj pain).ti,ab. (5876)

13 8 or 9 or 10 or 11 or 12 (40947)

14 4 and 7 and 13 (90)

15 limit 14 to english language (74)paste in search]

## **Embase (via Ovid)**

<1996 to 2013 October 30>

1 Ketamine/ (16774)

2 ketamine.ti,ab. (10221)

3 ketalar.ti,ab. (36)

4 1 or 2 or 3 (18305)

5 exp oral drug administration/ (69309)

6 oral.ti,ab. (355264)

7 5 or 6 (396669)

8 exp chronic pain/ (27887)

9 exp neuropathic pain/ (16227)

10 exp complex regional pain syndrome/ (4764)

11 (chronic adj pain).ti,ab. (23624)

12 (cancer adj pain).ti,ab. (7150)

13 8 or 9 or 10 or 11 or 12 (57547)

14 4 and 7 and 13 (164)

15 limit 14 to english language (140)

16 limit 15 to exclude medline journals (11)

## **Cochrane Central Register of Controlled Trials (CENTRAL)**

#1 MeSH descriptor: [Ketamine] explode all trees 958

#2 (ketamine or ketalar):ti 1295

#3 #1 or #2 1398

#4 MeSH descriptor: [Administration, Oral] explode all trees 19126

#5 (oral and administration):ti,ab 13069

#6 #4 or #5 28014

#7 MeSH descriptor: [Chronic Pain] explode all trees 143

#8 (chronic and pain):ti 2618

#9 (cancer and pain):ti 803

#10 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees 185

#11 neuropathic pain 965

#12 #7 or #8 or #9 or #10 or #11 4290

#13 #3 and #6 and #12 10

## CRD HTA, DARE and EED database

MeSH DESCRIPTOR Ketamine EXPLODE ALL TREES = 27

OR Ketalar in all fields= 0

## Grey literature and ongoing trials

- [NICE Evidence](#)
- [Health Canada - Clinical Trials Search](#)
- [metaRegister of Controlled Trials \(mRCT\)](#)
- [ClinicalTrials.gov](#)

## Manufacturers' websites

[Pfizer](#)

Ketamine or Ketalar

## *Evidence selection*

This evidence summary has included literature reviews, randomised controlled trials (RCTs), a case series of n-of-1 trials, and observational studies that have investigated the efficacy and safety of oral ketamine for treating chronic pain. Trials assessing oral ketamine in people with chronic cancer pain or chronic pain in palliative care were excluded because these were considered to be outside the scope of this evidence summary.

Two placebo-controlled RCTs and 1 case series of n-of-1 trials were identified as relevant. Two of the studies included adults with chronic neuropathic pain and 1 included adults with trigeminal

neuropathic pain. Two case series in adults identified by the initial search were also included because they had longer treatment durations.

No RCTs in children or young people were identified. A phase I pilot study identified by the initial search was included because this assessed the efficacy and safety of oral ketamine in young people with chronic pain.

## Changes after publication

### June 2014:

On 10 June 2014, the Parliamentary Order reclassifying ketamine as a class B drug came into force. Ketamine is not being rescheduled immediately. In line with the Advisory Council on the Misuse of Drugs' (ACMD) advice, the Home Office will carry out a public consultation later this year to assess the impact of rescheduling ketamine to Schedule 2. A final decision on the appropriate schedule for ketamine will be made after the consultation. Until then ketamine will remain a Schedule 4 Part 1 drug. The description of the regulatory status of ketamine has been updated within the evidence summary to reflect this.

### March 2014:

In December 2013, the Advisory Council on the Misuse of Drugs recommended that ketamine be upgraded to a class B drug and, subject to the outcome of a public consultation, a Schedule 2 drug. This recommendation has been accepted by the Government. The Order reclassifying ketamine as a class B drug will shortly be laid in Parliament and it is expected that reclassification will take effect in June 2014 subject to Parliamentary approval. After reclassification, ketamine will remain a Schedule 4 Part 1 drug until a decision is made, after the public consultation, on the appropriate schedule in which it should be listed. The description of the regulatory status of ketamine has been updated within the evidence summary to reflect this.

## About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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