Sublingual ketamine in chronic pain: service evaluation by examining more than 200 patient years of data

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Abstract
I present more than 200 patient years of observational data, including Brief Pain Index (BPI) outcomes on patients who have found sublingual ketamine useful to help manage their pain symptoms. Data was obtained from our Pain Audit Collection System (PACS), a review of the local Electronic Patient Record (EPR) and a separate bespoke database. The observations and treatment took place at an NHS district general hospital multidisciplinary pain clinic in England from 1 January 2000 onwards. Data was locked down on 1 March 2012 to allow analysis to be undertaken. Out of 249 patients tried with ketamine, 95 patients found it of little use on the day that they tried it. A further 107 patients took ketamine for as little as one month up to as long as seven years before stopping it. At the time of data analysis, 47 patients were still taking sublingual ketamine. 32 of these 47 patients had been taking sublingual ketamine for more than two years. The PACS Treatment Assessment Form consists of the BPI questionnaire and also asks one additional question: ‘In the last week, how much relief have pain treatment or medications, obtained from this clinic, provided? Please circle the one percentage that most shows how much relief you have received.’ In the 32 patients, who had been taking ketamine for more than two years, ketamine did not consistently improve BPI scores, but these patients did report pain relief when taking ketamine. The modal pain relief score reported by each patient was determined. The mean of all 32 modal pain relief scores was approximately 56% pain relief. As ketamine was often tried in combination with other pain treatment modalities, the observations made may be confounded by the effects of other pain treatments. At the doses used in my practice, no patient in this series has developed ulcerative cystitis. I conclude that when used carefully, low-dose ketamine can have a useful role to play in the management of chronic pain.

Keywords
Ketamine, chronic pain, service evaluation, long-term safety data

Introduction
Ketamine is a drug of abuse, a dance-floor drug and a date-rape drug. It is also an anaesthetic drug with analgesic properties. The use of ketamine to manage chronic pain is controversial. Anecdotal case reports suggest that ketamine may be a simple and useful treatment option to help patients manage their chronic pain, particularly when other treatments have not proved useful. On the other hand, concerns have been raised that ketamine can cause liver and urinary tract damage and critics also point to a lack of gold standard randomised controlled studies to support its use and to a lack of long-term safety data. In a review of scientific evidence for acute pain

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management, the findings of a working group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine supported the use of ketamine in some acute pain situations. With respect to chronic pain, opinions in review articles have ranged from ‘… in situations where standard analgesic options have failed, ketamine is a reasonable third line option’ to ‘while the current literature provides evidence for acute relief of chronic non-cancer pain, information supporting the efficacy and tolerability of ketamine in the long-term treatment of chronic pain is extremely limited’. Arguments are also made that any benefit patients experience are probably placebo (Wells, C., ‘communication’ on pain consultants Google group).

Patients attending my chronic pain service are offered a range of treatment modalities, including Transcutaneous Nerve Stimulation (TNS), acupuncture, group-based and individual exercise programmes, pain management programmes and injection-based approaches, and are offered input from psychology and occupational therapy. Onward referral to a tertiary centre is also possible and, of course, drug interventions are also offered. In 1999, the evidence-based drug treatments in vogue were capsaicin ointment, amitriptyline (and other antidepressants), and carbamazepine (gabapentin was being used on an unlicensed basis back then, as were other anti-epileptics). At that time, the majority of drugs available for chronic pain were unlicensed, or had very specific licensed indications. Once these drugs had been tried, there were few other drugs to try apart from opioids, and much like today, clinicians and patients alike were wary of commencing these. Inevitably back then, as is the case currently, some patients were not prepared to accept that there was nothing else that could be done for their pain, and these patients were not ready to progress to a pain management programme.

It was in this context that I came across the 1999 publication by Batchelor where he recounted his experience of using the drug in patients over a period of five years. Shortly after publication of this article I tried ketamine in a patient who had tried all other treatment modalities available to me. The patient reported good pain relief so I have continued to try other patients with this drug over the years. As I routinely collect outcome data for all my patients using the PACS database, I decided after several years to evaluate outcomes of patients who have been through my service and tried ketamine. After this initial evaluation and following the reports of ketamine-induced ulcerative cystitis, I then created a bespoke simple database to allow me to systematically track who had received ketamine and how they had fared as part of a continuous audit process. As there is a dearth of information regarding long-term outcome data in patients who use ketamine as an adjunct in their management of chronic pain, I hope this paper will shed some light on this neglected area of study.

Methods

The clinical director of our local research and development department has confirmed that because this paper consists of service evaluation and audit, no ethics committee approval was required.

Ketamine administration

After appropriate counselling in the outpatients (where patients are given a patient information leaflet and are informed that ketamine is also known as a drug of misuse, a date-rape drug, a dance-floor drug, a horse anaesthetic and a human anaesthetic which might make them hallucinate and has a poor success rate in the management of chronic pain), patients are listed for a trial of oral ketamine (technically it is sublingual administration but it is easier for everyone to say the word ‘oral’ rather than ‘sublingual’). As patients have access to the Internet these days, I feel they are better off hearing this information from me rather than reading
about it online and then possibly feeling that I was hiding this information from them. Most patients are considered to be eligible for consideration for ketamine treatment. Patients with a history of substance misuse and female patients of childbearing age who are yet to complete their family are not usually offered this treatment modality.

Patients who wish to try ketamine are asked to attend the Day Surgical Unit (DSU) on the day that I carry out my injection list. The ketamine is administered prior to starting the injection list. If possible, patients are admitted to a quiet side room on our DSU. I ask patients to take all their regular painkillers as normal (so I can judge better the interaction between these drugs and the ketamine). Prior to asking a patient to sign their ‘NHS Informed Consent Form 3’, I ask the patient to numerically rate their pain score (0–10) and I make a note of this. I then administer the sublingual ketamine (Pfizer Limited, Sandwich, Kent CT13 9NJ, UK). It is the intravenous preparation that I use. For many years it has been the 100 mg/ml preparation that has been used but, more recently, manufacturing has been relocated and stocks are running low (personal communication from pharmacy) so currently we have been using the 50 mg/ml preparation. The usual dose is 20 mg and I ask the patient to hold it sublingually as long as they can, and inform them that they can swallow if they feel they are going to drown in their own saliva. After completing my injection list I return to review the patient. I ask the patient if they have had any benefit and ask them to numerically rate their pain score again on the same 0–10 scale. It is clearly easier to judge the utility of the ketamine if the pain is constant rather than episodic.

Patients are asked to complete a ketamine treatment agreement (Appendix A) if they appear to have found the ketamine helpful. One copy of the agreement is given to the patient and the other is filed in the medical records. I ask patients to demonstrate using tap water that they can successfully draw up and self administer the correct amount of drug before discharge. Patients are given a 30-day supply of ketamine in a standard NHS drug dispensing bottle (the shelf life of ketamine in this bottle is only 30 days – personal communication from Trust pharmacist). The usual dose suggested to the patient is 20 mg to be taken three times per day via the sublingual route. Patients are advised that they can experiment a little with the dose but to not exceed the total daily dose of 60 mg per day. Suitable dose options could be 30 mg bd or a single maximum dose of 40 mg, with the remaining 20 mg either split into two doses of 10 mg, or one dose of 20 mg. Patients are requested to self-assess which dose regime appears to suit them and they are reviewed in the clinic four weeks later. If the ketamine is still helping at this stage, patients are initially reviewed again at three months, and if all is well at that point, patients are then reviewed on a six-monthly basis and repeat prescriptions issued at each outpatient visit. The medication is dispensed by the hospital pharmacy on a monthly basis.

Data collection and analysis

I routinely attempt to collect outcome data for all patients who attend my service by means of using the PACS Treatment Assessment Form. This form consists of the BPI questionnaire and it also asks three additional questions, one of which is: ‘In the last week, how much relief have pain treatment or medications, obtained from this clinic, provided? Please circle the one percentage that most shows how much relief you have received.’ Data from the paper form was then entered onto the PACS database by either myself or the specialist pain nurse. After carrying out my first audit in 2004, it became apparent that extracting information would be easier by setting up a simpler bespoke database. The spur to design and use such a database came in 2008 when reports emerged of renal tract problems associated with ketamine use. Microsoft
Access® was used to design the database: data collected included the age, sex and name of the patient who had tried ketamine, the date they started treatment (data field [on it since]) and whether they were still on treatment. If the patient was still receiving ketamine treatment, a calculation was made of how many days the patient had been taking the ketamine by building the following expression in the field cell of a query: Int((Now()–[on it since])) . Summing this value for each patient and dividing by 365 calculated the total number of patient years of treatment. The audit standard for the 2008 audit that I carried out was that no patients receiving ketamine would have ulcerative cystitis. After consultation with a urology consultant, urine dipstick testing and biochemical profile were deemed to be the screening investigations of choice. Patients attending the clinic for ketamine review were informed of the possible issues and they were offered screening. Following the audit, the bespoke database continued to be used as a convenient means of being able to systematically audit patients who had tried ketamine.

The PACS database also has a function that allows BPI scores to be viewed graphically as well as in tabular format. Both ways of viewing the data were extracted for the 32 patients who had been taking ketamine for more than two years. A separate worksheet for each patient was created in a Microsoft Excel® spreadsheet. Each worksheet contained the PACS data for each patient. The modal value for pain relief was determined for each patient. It was ensured that the modal value was only determined for observations made on dates after the ketamine was commenced. The modal value was put in cell A1 of each worksheet and the mean of all modal values was obtained. A copy of the spreadsheet will be made available online with this paper. In addition, the following information was collected using PACS and the EPR as source data: starting ketamine dose and current treatment dose; clinical diagnosis; biochemical profile where available; side effects noted; and other snippets of medical history where deemed relevant.

Results

Figure 1 illustrates how patients progressed after having sublingual ketamine administered to them. As can be seen, at the time of data lockdown I had tried 249 patients with sublingual ketamine. 95 patients did not find it of any help at all when they were reviewed several hours after having it administered to them. 107 patients appeared to find the ketamine of some benefit, but abandoned the treatment at a variable interval after having been commenced on the drug. The bulk of patients who abandoned treatment did so within the first two years of trying the medication. Unfortunately, I did not systematically collect the reasons why the ketamine treatment had been abandoned in these patients. Eight patients who had been on regular ketamine died during the period being analysed. I am able to provide on request a list of when the ketamine was stopped. 47 patients were still taking ketamine when the data was locked down.

Figure 2 shows the age and sex distribution of my 47 patients who were taking ketamine when the data was locked down. Figure 3 lists the diagnoses of the 47 patients still taking ketamine. As can be seen, patients with a range of diagnoses seem to have found some benefit.

Of the 47 patients were still taking ketamine, 32 of these patients had been taking sublingual ketamine for more than two years. I looked at these 32 patients in greater detail. Table 1 shows the duration of treatment in these 32 patients, the age at which treatment was started, the sex of the patient, the starting dose of ketamine, the current dose of ketamine and the mode value of all the pain relief scores reported by each patient. The total duration of patient treatment was calculated to be more than
200 years. If ketamine treatment was successful, the average pain relief that patients reported was calculated to be 50–60%.

The standard for the 2008 ketamine audit was that no patient should have had ulcerative cystitis or renal impairment as a consequence of taking ketamine. This standard was met and Figure 4 highlights the findings of this audit. At that audit, it was noted that 5 out of 179 patients had experienced hallucinations of some sort and that two patients thought they were getting more forgetful. Since that audit, one patient has stopped taking ketamine because they were concerned that their memory was failing.

Figure 1 – Flow chart illustrating how patients progressed after taking ketamine

249 patients try sublingual ketamine.

Did it help on the morning of taking the drug?

No

95 patients find it of no use on the morning of trying the drug.

Yes

Is patient still taking the ketamine?

No

107 patients took ketamine over a time period from as little as one month to up to as long as seven years before stopping.

Yes

47 patients are still taking the ketamine.

32 of these 47 have been taking it for more than two years.

8 of these patients stopped taking ketamine because they died – 4 cancer-related deaths, 1 patient with post-stroke pain died, 1 patient had a diabetes-related death and 2 patients died from other causes.

Patients may also have stopped taking ketamine if the drug no longer helped them or if they got side effects.
Figure 2 – Age/sex distribution of 47 patients taking ketamine. Age is the age at which the ketamine was started, not the patients' current age.

Figure 3 – Diagnoses of patients currently taking ketamine

LOW LEG PAIN
BACK AND NECK PAIN
ARTHRITIS AFTER NON SPECIFIC URETHRITIS
ANKYLOSING SPONDYLITIS – COLECTOMY FOR ULCERATIVE COLITIS
MULTIPLE JOINT PAINS
RETROPERITONEAL FIBROSIS PAIN
HEADACHE AFTER ENCEPHALITIS
REMITTING MULTIPLE SCLEROSIS (MS) - EPISODIC PAIN ? DUE TO MS
PAGET'S DISEASE PAIN
CHRONIC PANCREATITIS
POST HERNIORRHAPHY PAIN
POST CIRCUMCISION PENILE PAIN AND PERINEAL PAIN FOLLOWING
REVISION PENILE SURGERY
POST LAPAROTOMY ABDOMINAL WALL PAIN
POST LAMINECTOMY PAIN
POST THORACOTOMY PAIN (THORACOTOMY FOR SCHWANNOMA)
POST HYSTERECTOMY WOUND PAIN
CRPS POST CMC FUSION SURGERY
Table 1 – Patients who have been taking ketamine for more than two years: breakdown of age treatment started, sex, duration of treatment, starting dose of ketamine, current dose of ketamine and modal pain relief.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Treatment duration (in days)</th>
<th>Age ketamine was started</th>
<th>Sex</th>
<th>Starting dose of ketamine</th>
<th>Current dose of ketamine</th>
<th>Modal pain relief (%)</th>
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<tr>
<td>Patient 1</td>
<td>4448</td>
<td>39</td>
<td>male</td>
<td>10 mg tid</td>
<td>15 mg tid</td>
<td>70</td>
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<td>30 mg tid</td>
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<td>20 mg tid</td>
<td>80</td>
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<td>Patient 4</td>
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<td>35</td>
<td>male</td>
<td>1mg tid</td>
<td>15 mg bd 25 mg od</td>
<td>70</td>
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<td>36</td>
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<td>30 mg tid</td>
<td>60</td>
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<td>Patient 6</td>
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<td>48</td>
<td>male</td>
<td>10 mg tid</td>
<td>50 mg nocte</td>
<td>70</td>
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<td>Patient 7</td>
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<td>15 mg tid</td>
<td>90 mg in 24 hours</td>
<td>40</td>
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<td>Patient 8</td>
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<td>female</td>
<td>75 mg 5 times per day</td>
<td>90 mg 7 times per day 140 mg nocte</td>
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<td>30 mg tid</td>
<td>60</td>
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<td>30 mg tid</td>
<td>60</td>
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<td>male</td>
<td>20 mg tid</td>
<td>30 mg bd</td>
<td>60</td>
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<td>30 mg tid</td>
<td>50</td>
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<td>30 mg tid</td>
<td>70</td>
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<tr>
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<td>female</td>
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<td>90 mg in 24 hours</td>
<td>40</td>
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<td>30 mg tid</td>
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<td>60</td>
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<td>60</td>
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<td>30 mg qid</td>
<td>60</td>
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<td>30 mg tid</td>
<td>50</td>
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<td>75 mg nocte</td>
<td>50</td>
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<td>30 mg tid</td>
<td>90</td>
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<td>20 mg tid</td>
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<td>20 mg tid</td>
<td>60</td>
</tr>
<tr>
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<td>female</td>
<td>20 mg tid</td>
<td>20 mg tid</td>
<td>90</td>
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<tr>
<td>Patient 27</td>
<td>1152</td>
<td>43</td>
<td>female</td>
<td>20 mg tid</td>
<td>40 mg mane 50 mg nocte</td>
<td>60</td>
</tr>
<tr>
<td>Patient 28</td>
<td>1096</td>
<td>56</td>
<td>female</td>
<td>10 mg bd</td>
<td>20 mg bd</td>
<td>50</td>
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<td>Patient 29</td>
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<td>male</td>
<td>20 mg tid</td>
<td>30 mg qid</td>
<td>50</td>
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<td>30 mg bd</td>
<td>30 mg tid</td>
<td>60</td>
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<td>63</td>
<td>female</td>
<td>20 mg tid</td>
<td>20 mg qid</td>
<td>20</td>
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<td>Patient 32</td>
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<td>36</td>
<td>male</td>
<td>20 mg tid</td>
<td>30 mg tid</td>
<td>50</td>
</tr>
</tbody>
</table>

Total patient days of treatment: 74,277

Average modal pain relief: 50%
* This patient was inadvertently given this patient number early on in data analysis – therefore, in order to not have to renumber all patients and confuse myself, identity maintained as patient 14.

Figure 4 – Results of 2008 audit

2008 Audit Standard:
No patient on Ketamine should have ulcerative cystitis
Or evidence of renal impairment

3 patients have macroproteinateuria due to Diabetes

3 cases of unexpected microhaematuria – investigated by standard protocol (i.e. cystoscopy, ultrasound and IVP) – nil found in 2, 1 had an inverted papilloma resected which was presumed to be source of bleeding.

1 known recent UTI

Some patients known to have renal abnormalities:

One case of retroperitoneal fibrosis; one case of solitary kidney; one known cyst of lower pole of kidney

5 hallucinations out 179 patients
2 forgetfulness out of 179 patients

(At this point 179 patients had tried Ketamine and 44 were taking it regularly)

Discussion

Although the randomised controlled trial is the gold standard experimental design for testing a novel intervention, many areas of clinically important knowledge are best, or most efficiently, informed by high-quality observational data. I make no claim to have provided randomised controlled information or evidence in this paper – I have merely written about what I have observed when my patients have tried sublingual ketamine in an attempt to help them manage their pain. This data therefore comes with all the warnings and caveats that apply to this type of information.

Anyone thinking about prescribing ketamine in the way that I have needs to answer for themselves the following questions:

• Does ketamine work?
• Is it safe?
• How do I use it?

This data suggests that about 1 in 5 patients seem to get some sort of benefit from ketamine in the long term. There is clearly a huge placebo effect and this is manifest by the number of patients who abandon treatment within the first few years of trying the drug. It is argued that the 1 in 5 patients who appear to have a long-lasting response to ketamine are also demonstrating a placebo response (Wells, C., communication on pain consultants Google group). While this may be the case, I would point out that the same patients did not elicit the same remarkably persisting ‘placebo’ response when they tried other evidence-based drugs like amitriptyline, duloxetine, gabapentin or pregabalin beforehand.

When patients did report benefit, the average pain relief that patients reported was calculated to be 50–60%. However, the benefit reported does not appear to translate itself in the form of better BPI scores. Eyeballing the data does not show any clear pattern or trend with respect to pain scores or interference with various elements of the BPI. The question therefore that has to be asked is that if ketamine is not improving BPI, what is it really doing?

It is possible that ketamine may be improving the low mood which often accompanies patients who have chronic pain. There is randomised controlled evidence that intravenous ketamine can act as an acute antidepressant with effects that appear to persist long after the drug is considered to have cleared from the body.\textsuperscript{16,17}

I have considered the possibility that the effect seen is due to this small group of patients having become physically dependent on ketamine. On the other hand, patients who abandoned ketamine therapy within the first two years did not report an abstinence syndrome. Anecdotally, over the years, patients who have been on treatment longer than two years occasionally run out of ketamine and sometimes have to wait a few days before having the medication dispensed. To the best of my knowledge, these patients have also not reported an abstinence syndrome, although they do report their pain gets worse. In conclusion, it is unlikely that physical dependence has occurred.

The lack of long-term safety data for a drug such as ketamine has been of concern to some authors.\textsuperscript{6} The limited data I present appears to show that at low doses there does not appear to be any easily observable harm stemming from the use of ketamine. Currently, the total daily dose for most of my patients does not tend to exceed 120 mg per day, with the odd exception. There is evidence to suggest that liver and urinary tract side effects are dose-dependent phenomena.\textsuperscript{18} This is reassuring – after all, we still use paracetamol for pain relief, even though we know that in overdose, the side effects can be serious. There is also data to suggest that high doses of ketamine may actually cause hyperalgesia,\textsuperscript{19} so there are several reasons to not escalate the dose of ketamine.

My data suggests that hallucinations are not that common at the dose used. If they do occur, they are not usually too intrusive, although one patient had to decrease her dose to 1 mg three times per day. Higher doses made her very sleepy and even on this lower dose she would experience some visual disturbances (e.g. the ceiling looked like syrup, which would drip to the floor). This patient discontinued her treatment after almost two years after not attending for follow-up. Another elderly patient saw an apparition of her deceased mother standing at the bottom of her hospital bed when
she tried ketamine for the first time. This was clearly unsettling for her because her mother had passed away many years ago. Needless to say, this patient did not progress to taking ketamine on a regular basis. Another regular user of ketamine reported that once, after having taken ketamine on an empty stomach, and subsequently having breakfast, that his breakfast cereal looked like rocks.

It is argued that if the beneficial effect of ketamine is a placebo effect, then there is clearly an opportunity cost associated with my activity. On the other hand, if this is a placebo effect, this ‘placebo’ effect has satisfied my patients for a considerable period of time and I have helped my patients to avoid some of the riskier interventions that we pain physicians have at our disposal and that they may not necessarily have wanted to pursue.

Unfortunately, there does not appear to be a consistent pattern as to what types of pain ketamine is most helpful for. Some would argue that snake oil appears to have similar breadth of beneficial effect.

Some proponents of ketamine prefer the use of an intravenous infusion approach, rather than the sublingual approach. In 2012, Patil and colleagues published a five-year retrospective analysis of 49 patients with chronic pain who had undergone a total of 369 outpatient ketamine infusions between them. They concluded that ‘in patients with severe refractory pain of multiple aetiologies, subanaesthetic ketamine infusions may improve Visual Analogue Scale scores’. In half of their patients, relief lasted for up to three weeks with minimal side effects. Some advocates of ketamine have gone even further and used substantial doses of ketamine to induce a coma in an attempt to ‘reboot’ the central nervous system, but death is a rare complication of this procedure – hence my preference for using the sublingual route at a fraction of these doses. While I hope that the following anecdote will not encourage patients to try this, I would like to report that one of my patients inadvertently took ten times her normal dose – 200 mg rather than 20 mg – while on holiday abroad – this happened because she lost her normal oral syringe and was unfamiliar with the markings and units on the replacement syringe she obtained from the pharmacy where she was abroad. She reports that her family said she was unconscious for 18 hours, but recovered with no ill effect, apart from suffering ‘a bit of a fright’. Following this incident, I stopped prescribing ketamine for this patient because she had previously reported inconsistent benefit and, in any event, she had stopped taking it after this incident.

I continue to train and obtain treatment agreements and consent from patients myself prior to commencing them on sublingual ketamine. While I am now sufficiently confident that ward staff could probably be trained to do this, there isn’t enough volume per year to ensure that they would be regularly exposed to carrying out this activity. Furthermore, local circumstances dictate that I can’t always guarantee that the same staff will be available on the ward – so while training the patient and securing the treatment and obtaining informed consent can be time consuming, the benefit is that this expertise stays with me and at least I know I have said the same consistent thing each time.

In the NHS setting, the income this activity attracts under the payment-by-results regime is the income that is obtained when the patient is admitted as a day case to try ketamine. Subsequent income is generated from each outpatient attendance. The income generated from the day-case attendance depends on patient comorbidities – some recent trials have earned £221–385 of income for my unit. At the time of data
lockdown, my pharmacy informed me that the cost of supplying ketamine to the 47 patients was about £25 000 per annum. This equates to approximately £530 per patient per annum, or about £44 per month.

Conclusion
The long-term use of low-dose sublingual ketamine in chronic pain appears to be safe. Some patients find it very helpful for their pain when other drugs have not worked. To date, using it long term has not appeared to cause too many problems.

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Conflict of interest disclosures
Over the years I have attended numerous lunches and dinners paid for by many different drug companies and over the years have also been the recipient of ‘Post-its’, pens, memory sticks, mugs and so on. Under the payment-by-results regime, my Trust will earn money for each patient who attends to try ketamine and who then attends regularly to be monitored and to pick up their ketamine prescription.

Disclaimer
While I have made every effort to ensure that there is no misleading data or statement in this paper, and that all drug doses are presented accurately, readers are advised to ensure that drug usage as described in this paper is followed in conjunction with the drug manufacturer’s own literature. I do not accept any liability for any problems that may arise from following the described medication regimen.

Note on supplementary files
To read source data please request from the author by emailing: varunj@rocketmail.com.

References


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