An evaluability assessment to explore policy change on the use of Ketamine for treatment of depression and addiction in Scotland

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SUMMARY

Scotland is experiencing a drug death crisis from licit and illicit substances, e.g. opioids, cocaine, benzodiazepines (Scottish Government, 2023). ~93% of Scottish drug deaths involve 2+ substances (polysubstance use) 9Scottish Government, 2022). Medical treatment for substance use is limited to a single opiate addiction, that is ineffective for polysubstance misuse (Bunting, 2022; National Academy of Sciences, 2019), and there are no interventions designed specifically for polysubstance use (Compton, 2021). Psilocybin has transdiagnostic potential across a range of licit and illicit substance misuse (Kocarova et. al., 2021). Polysubstance users are entering remission with a single underground psychedelic ritual group experience (NHS Lanarkshire, n=3). Evidence (n=866) indicates communal experience and ritual (communitas) improves the outcomes of psychedelic medicine [7].

The aim of the research was to carry out a formative evaluation of ketamine assisted therapy (KAT) treatment policy in Scotland using the case study of the Eulas Clinic, based in Hamilton, Scotland. We aimed to assess the protocols in place and stakeholder needs, in order to develop the rational for larger evaluations and research collaborations between the local health board, the Scottish Government (NHS) and the wider medical community on the impact of this novel psychedelic treatment.

Due to the nature of the proposed methods the research was not reliant on Eulas being granted a license, although we had anticipated that it would be granted during the research timeframe which would have enabled us to engage with stakeholders accessing the service. However, Eulas clinic were only granted a license in the final weeks of the project, and they were unable to start operating due to the Health Improvement Scotland requirements that they also receive a UK Home Office controlled drug license (see below for more details). As a result, we were unable to engage with end users who have experience of this therapy in Scotland. However, we did engage with end users who have experience of using this therapy, and trying to access it in Scotland (see case studies in our other report and below).

Additionally, as we started to engage with stakeholders it became evident that there was a lack of understanding and coherence within the sector or how and why ketamine has become an option in the treatment of depression and addiction.

As a result, the project shifted from being an evaluability assessment of Eulas Ltd., to a wider pre-evaluability assessment of the current policies and practices in place regarding Ketamine treatment in Scotland, with Eulas used as a case study. We outline our outcomes based on the deliverables we proposed in the initial funding application.

DATA COLLECTION

Of the psychedelic medicines, only ketamine is licensed for use in the UK by the Medicines & Healthcare products Regulator Agency (MHRA) as it is already used in hospitals as an anaesthetic medicine, in high doses. Ketamine comes in three forms (isomers): arketamine, esketamine, and racemic ketamine: a mixture of arketamine and esketamine. Arketamine is generic to produce, and is routinely produced in the UK for patient needs. Esketamine is a more recent isolate, and forms the basis of the only patented ketamine product on the market – Johnson and Johnsons Spravato© nasal spray.

Ketamine can be delivered to patients through multiple routes; intravenous (IV), subcutaneous, intramuscular and intranasal. Evidence suggests that for mental health treatment, racemic ketamine has the best health outcomes (Nikolin, Rodgers et al. 2023) and that the best routes of administration are IV and intranasal (McIntyre, Rosenblat et al. 2021).

There was some initial confusion during the scoping element of the project, and a lack of clarity on who are where were prescribing ketamine. In particular it was believed – to the extent it was reported on - that NHS Forth Valley were part of a trial site, however communication with the trial developer in England (Dr. Celia Morgan) confirmed that while conversations had started for a trial, due to regulatory differences in Scotland they were unable to set anything up in Scotland. While it is true that all Scottish NHS units have been given the go ahead to provide ketamine treatment, only two health boards – NHS Highlands and Islands, and NHS Lothian – have considered it, and this is as a replacement for electric convulsive therapy (ECT).

Another misconception was that the Johnson and Johnson racemic ketamine nasal spray Spravato© had Scottish Medicines Consortium (SMC) approval and would be the main route of administration. However all ketamine being delivered in Scotland is currently rketamine with intravenous/sub-cutaneous delivery. This came to light after our conversations with a clinical psychiatrist looking to introduce ketamine therapy to replace ECT in NHS Lothian. Their reason for not using Spravato© was based on cost: Spravato© currently costs in the region of £500 per dose compared to around £50 per dose of intravenous arketamine. However, SMC approval lapsed in 2022.

From these conversations, and the barriers and challenges as outlined below, the following 4-6 months were spent digging beneath the conflicting and contradictory messaging coming from different parts of the community. This involved interviews, workshops, literature reviews, and hundred of emails back and forth clarifying different aspects of the process and policies, including the behemoth of the University internal processes.

OUTCOMES/SUCCESS

The main outcome and success of this project is a deeper understanding of the policies and practices in place in Scotland for the provision of Ketamine therapy. A second outcome is a better understanding of how ketamine therapy should be conducted in order to provide the best outcomes for patients.

ORGANISATION

Currently the types of organisations that are offering ketamine IV infusion treatment are for profit limited private companies or NHS boards/Trusts. As it stands the NHS is struggling to meet current demands of new treatment types and technologies, whereas small private companies have the agility to meet the demand more quickly. Eulas Clinic is different to the other private providers of IV ketamine infusion as their business model is a social enterprise model where funds are reinvested into the business to try and reduce access costs to the community. Several NHS Trusts/Boards provide ketamine but only for patients in severe psychological distress, that have been sectioned against their will, as an alternative to electroconvulsive therapy (ECT); NHS Highlands and NHS Midlothian in Scotland, as well as NHS Oxford and NHS South London in England. NHS Oxford and NHS South London can provide off label access to ketamine for TRD but only for patients that live in the local area.

APPROVAL

There is some confusion between organisations providing licensing and the regulatory framework for ketamine treatment in Scotland. Clinics are required to obtain a license from Healthcare Improvement Scotland (HIS).

Healthcare Improvement Scotland (HIS) provides licensing of clinics. It is their decision to require an anaesthetist to provide ketamine treatment. The Home Office has stated that a controlled drugs license is not required for clinics to provide ketamine treatment, but HIS has demanded that a controlled drugs license be issued to give approval for Eulas Clinic to provide ketamine treatment. However, the Home Office is uneasy about providing a controlled drugs license without approval of services by HIS. These communication inconsistencies cause delays to the approval process. Further communication inconsistencies and delays from HIS have resulted in an 18 month approval process for licensing Eulas Clinic that is still not yet complete as Eulas Clinic awaits their

controlled drugs license from the Home Office (Eulas Clinic were only informed 12 months into the process that a controlled drugs license was required despite the Home Office providing a letter stating that they did not need one). Eulas Clinic have been able to stay afloat despite these delays and their adverse effects on clinic costs because they have an anaesthetist and a clinical psychiatrist on the board. It has cost Eulas Clinic ~£75,000 in startup fees as well as keeping the doors open throughout the delays caused by HIS. Any other organisation would have need to keep these trained professionals on a retainer leading to an additional projects cost of £100,000. Eulas Clinic is based in Hamilton, had they tried to setup their clinic in a city like Edinburgh or Glasgow the delays would have forced the business to close months ago due to increased overheads.

As it stands, the waiting list for ketamine treatment at Eulas Clinic is in the hundreds and they do not have the capacity to meet this demand due to the requirement of having an anaesthetist provide this treatment as anaesthetists are few and their costs high. If HIS, the Home Office, SMC and/or NICE were to get behind providing ketamine treatment then together they could streamline the process of ketamine clinic approval, redefine the regulations for ketamine treatment delivery that reflect the needs of patients without compromising on safety, and help to remove the burden of TRD on the NHS.

ACCESS AND DELIVERY

Racemic ketamine is used routinely in hospitals across the UK as an anaesthetic and for pain relief. Ketamine infusions for TRD are administered in much lower doses that have a low cost (<£50 per dose). The racemic ketamine is the least costly element of ketamine treatment. Private clinics as well as NHS Trusts in England may also require patients to undertake a treatment package that include ancillary medical checks and analyses that overinflate the price (e.g. MRI, blood sampling, etc) and are not required by ketamine clinics in other parts of the world. If these non-essential elements are removed, there still remains the requirement that anaesthetists provide the ketamine treatment, as prescribed by Healthcare Improvement Scotland and NHS Pharmacy at NHS South London. However, an anaesthetist is not required to administer ketamine to the most vulnerable of patients, patients that have been sectioned against their will and are being given ketamine as an alternative to ECT. In other parts of the world that are experienced with providing ketamine treatment for TRD and other disorders (e.g. USA, Germany, Japan) well trained nurses administer ketamine infusions.

On the surface it would seem that having an anaesthetist provide the ketamine infusion is the safest option but they are trained to look for problems that would arise when giving patients anaesthetic level doses of the medicine. For example, drip rate and anti-nausea medication are critical to the experience of the patient during ketamine infusions for mood disorders, as too fast and the patient can completely dissociate from their bodies as well as cause vomiting. These outcomes lead to decreased positive outcomes for patients and should not be ignored from patient care requirements.

In America, the healthcare provider that give ketamine treatment are equivalent to somewhere between a nurse and a doctor in the UK. They can provide the IV infusion, as a nurse could do in the UK, and they stay with the patient during the experience to ensure that they do not experience adverse effects and are able to pre-empt this happening based on their experience of giving this type of treatment. Anaesthetists are not trained in these crucial elements and their services over inflate the price of treatment, if they can be attained in the first place – anaesthetists are in demand and there are not very many of these trained specialists.

In the UK, the largest barriers to accessing ketamine for mood disorders are availability and cost and is predominantly only available to the wealthy. One of the patients in the case studies provided below was referred to NHS South London for ketamine treatment for TRD. NHS South London would not cover the costs of his treatment and referred Kendall to NHS Midlothian in Scotland but they do not provide that type of treatment. Kendall searched private organisations in the UK that charged anywhere between £1700 - £8000 for treatment. After reviewing all of his options, it was cheaper for Kendall to fly home to America from Edinburgh every 3

weeks where he knew that medical staff would be able to support his needs at a reasonable cost through private healthcare (~£500 per trip).

Aside from cost, there is inconsistency in access to ketamine treatment on the NHS as described above with few sites providing access for TRD and NHS website information is lacking and seemingly unsupportive of ketamine treatment on their website. This may be partially due to stigma. For example, both patients that provide a case study below tried to access ketamine through their GPs and each tried several. Due to stigma and ignorance of ketamine treatment amongst GP surgeries these patients often felt belittled, were told to try some other treatment or were treated with suspicion that they may be drug addicts seeking ketamine for recreational use despite having all of their documents and letter from their care staff in America, as well as through Prof Allan Young (Kings College London) at Maudsley clinic, NHS South London.

At Maudsley Clinic, patients can be referred by their treatment team (internationally or locally), through the NHS and through self-referral. Where the patient already has a good healthcare team where talking therapies are provided, Maudlsey Clinic does not have to provide the talking therapy element. HIS requires that Eulas Clinic provide talking therapies to patients regardless of the treatment team in place that increases the cost of treatment to patients, as well as distress to the patients that may have already formed a safe and reliable therapeutic environment. These discrepancies are a further barrier to treatment.

OUTCOME

Currently, ketamine treatment allows patients to function normally, but ketamine infusions are required to retain that health outcome (~30%). However, when provided alongside good talking therapies the rate of remission can be 40-50% (Prof. Mario Juruena, Maudsley Clinic, NHS South London).

For substance use issues, ketamine has shown effective therapeutic potential for alcohol, cocaine and opioids (Krupitsky 2002; Ezquerra-Romano et al. 2018; Jones et al. 2018; Mollaahmetoglu et al. 2021; Grabski et al. 2022; Kelson et al. 2023), as well as treatment resistant depression. Participants in the research into ketamine treatment for substance use issues, where participant information was made clear, had a mean age range from 27.5 to 53 years and were primarily male (61%-100% across robust studies in the literature).

There is no coherent information on the use of ketamine to treat other addictions such as methamphetamine use disorder. For this reason, ketamine therapy for polysubstance use issues should be restricted to patients where the substance used disorders comprises alcohol and/or cocaine and/or opioids, but not in the presence of methamphetamine. In the United States of America, ketamine can also be used to treat nicotine addiction (e.g. the Mood Center) despite there only being limited evidence to treat this disorder in rats. Classical psychedelics, such as psilocybin and LSD, have broader applications in treating addictions as well as mental health co-morbidities, and therefore are likely to have better outcomes for polysubstance users (Kocarova et al. 2021).

Ketamine for substance use in EU countries, a shortlist:

- HIVE (Malta) – Web: Evidence based ketamine assisted psychotherapy retreat (hive.bio)
- Key Clinic (Poland) – Covered by insurance. Web: KeyClinic Centrum Psychiatrii i Psychoterapii Warszawa
- Paracelsus Recovery (Switzerland) – Web: Luxury Rehab Clinic in Switzerland | Paracelsus Recovery (paracelsus-recovery.com)
- Satori (Spain) – Web: Satori Recovery: Luxury Addiction Rehab in Spain.
- Silva Wellness (London) – Web: Silva Wellness | Ketamine Assisted Therapy London

LIVED EXPERIENCE OF END USERS

Here we present two brief case studies, in their own words, of people who have used ketamine for treatment depression and a rare psychiatric disorder. These participants were recruited via the clinics.

PARTICIPANT A

From relatively early in my childhood (I think around 6), I was taking medication and going to counseling to regulate my mood. Anxiety and anger were the main maladaptive traits that were targeted. However, as I moved into early adolescence, it was clear that I was not responding and was fairly unwell by any biopsychosocial definition of mental (or physical, for that matter) health. However, at around age 11 or 12, I was introduced to intranasal ketamine treatment after being diagnosed with fear of harm disorder (FOH). The syndrome is a phenotype of bipolar disorder that stems from a psychological response to a physiological inability to regulate body heat. The symptoms are wide-ranging, from heating-related sleep disruptions, inability to tolerate high heat, profuse sweating, mood instability, poor self-esteem regulation, poor frustration tolerance, and executive function deficits (issues with task start/competition, poor handwriting, difficulty getting past small details to see the big picture, etc.). The ketamine treatment, basically overnight, solved all these issues, as the ketamine has an epigenetic effect, effectively turning on the dysfunctional genes that regulate body heat. Put simply, I went from being unable to maintain homeostasis and thus regulate my mood, sleep, cognition, and executive functions to being able to do so. Of course, I have lingering issues from the trauma of living a disordered life and still some issues, especially with handwriting, but almost immediately after starting the ketamine treatment, I could live my life normally.

However, this makes it essential that I receive potent ketamine in line with the prescribing methods outlined for the condition. I.e., ketamine with a sufficient dose and potency (the half-life tends to be quite short) delivered intranasally or sublingually. This presents issues, as my desire has always been to live abroad, experience different parts of the world, and explore my curiosities about different cultures. The realities of ketamine being a controlled substance in many countries, and also my diagnosis being a novel one that requires off-label prescription, make things hard in terms of moving around. Generally, when considering a move for schooling or work I have to first do extensive research to find a prescriber. When moving to Edinburgh, we did months of research that summer and sent several emails that were not well received before finding a sympathetic prescriber. That enabled me to be in the UK. When moving to Germany, the process was somewhat easier as my prescriber could leverage their network to find a colleague in Dresden who was happy to help. The process was much simpler there because ketamine is less controlled, so my prescribers colleague was able to communicate with the German pharmacy system, which was happy to oblige if I paid the fees to help cover the costs of starting production. Accessing ketamine is a prerequisite before I can make a move, but overall, it has not been overly challenging, but it can take some time and stress to get set up. Thankfully, I am in a position to pay the costs associated with ketamine treatment (£140-200/month depending on country usually), but paid medical treatments go; they are not high.

PARTICIPANT B

I have been receiving ketamine infusions in the United States for over a year and a half as part of my treatment for Major Depressive Disorder, General Anxiety Disorder, and Panic Disorder.

My psychiatrist first introduced me to ketamine infusions in fall of 2022 as a last resort, after seven different antidepressants failed at treating my illnesses or improving my symptoms. Since then, I have been receiving ketamine infusions on a three week cycle, which is still the only treatment I have found effective; I am still trying out new medications and treatments with my providers.

Prior to starting my ketamine infusions, my condition was on a decline for ten months straight. At the start of the ten month period, my care team decided I was not in any condition to continue my study at university, forcing me into taking an Interruption of Study.

During that time period, I was experiencing severe emotional and mental instability due to my anxiety and depression, panic attacks and mental breakdowns at least two to three times a day, severe brain fog where I was having difficulty comprehending text and speech (numbers being nearly impossible to understand), nausea, and worst of all, occasionally waking up in a pool of blood at my desk. On some days, I would stab and cut my arm with a knife until I fell asleep. Feeling my emotional pain as physical pain was one of the few ways I coped with my suffering.

Separate from the self harming, I also struggled with physical pain throughout my upper body, caused by the psychological and emotional pain I felt. I was constantly fatigued and worn out from my symptoms and would sleep for 14-16 hours everyday.

By the ten month mark, my condition reached a point where my psychiatrist and psychologist agreed I was too unstable and a risk to myself and those around me. They stated they had no choice but to put me in involuntary hospitalization if this final treatment failed.

However, immediately after finishing my first ketamine infusion, I felt instant relief from the emotional and physical pain, an increase in energy, and mental clarity from the brain fog I struggle with. That night, I also experienced the best sleep I had in over ten months and woke up very refreshed the next morning. They had me go through seven more ketamine infusions in a two week period as an initiation phase, where I noticed a significant decrease in panic attacks, mental breakdowns, and suicidal thoughts after after each one. Another thing I realized was my circadian rhythm improving, sleeping 8-9 hours a day and waking up refreshed every morning.

All the symptoms continued improving and reached a point where we found out ketamine infusions could completely suppress my symptoms, as long as I received one every three weeks.

My provider and I settled for 3 week cycles in August of last year, due to my psychiatrist approving of my return to study in Scotland. I believe this three week cycle has the potential of being stretched out further. Just a couple of weeks ago, we found out I was experiencing almost no symptoms, even after the third week once we stopped the antidepressant I had been on.

CURRENT ACCESSIBILITY OF KETAMINE IN US AND UK

Accessibility of ketamine treatment in the UK has so far been the worst health care transition I experienced between countries.

First off, receiving ketamine for mental health was impossible in Scotland until now. And contacting the few private and NHS ketamine clinics in England last year, I received quotes ranging from £1,700-£8,000 for continuing care from the US.

After giving up on finding a realistic way of receiving ketamine infusion in the UK, I made the decision of spending £500 to fly 26 hours every three weeks, so I could continue receiving my ketamine infusion in the United States, fully covered by insurance. I was also offered the option of receiving ketamine infusions in Canada for around £140 without insurance. Ketamine infusions are so vital for retaining my wellbeing currently, the time and cost I sacrifice is worth the benefits of the treatment.

I also looked into ketamine clinics in countries around the UK and US telehealth services offering at-home ketamine treatment as alternatives.

I met with doctors at ketamine clinics in Spain, France, and Italy but faced the issue of language barrier. Regardless of how low risk ketamine infusions may be, I do not feel comfortable working with providers who I will have difficulty communicating with, even if they are less than a third of the pricing in the UK.

With the US telehealth service, receiving ketamine troches was almost too easy, highlighting the importance of some regulations. A doctor I met online for the first time prescribed eight 300 mg troches, alongside an extra 300mg for adjusting doses after just five minutes of speaking.

The telehealth service even changed my refill prescription to eight 800 mg ketamine troches after I mentioned 300mg was not providing the same benefits as my ketamine infusions. They did not require me to have another appointment with the doctor when making the change. For my second refill, I was asked to have a five minute phone call with the provider, which was not even a video visit.

INFUSIONS VS TROCHES

While ketamine troches are definitely more affordable and accessible than ketamine infusions, I have found ketamine infusions more reliable and consistent with the experience and benefits.
This is most likely due to having the ketamine infused directly into my bloodstream, which means I can consistently receive the same amount of ketamine every treatment.

With troches, since it is through oral membrane absorption, the bioavailability is much lower and each session varies greatly. I have noticed my sessions vary depending on what I ate, how much I exercised, and how much I stimulated my gums prior. And as mentioned, I require 800mg of ketamine in troches for the same benefit as my ketamine infusion, where I receive 50mg.

DIFFERENCE FROM ANTIDEPRESSANTS

From my experience, the largest benefit of ketamine treatment is how quickly the benefits occur. With traditionally antidepressants, I have always been told it would take a month or two before noticing the benefits, if any. And unlike antidepressants, ketamine does not come with any side effects such as worsening of depression or anxiety, increase in suicidal thoughts, numbing of emotions, worsening sleep patterns, etc.

The way I would describe ketamine infusion is a brain spa, where I come out of the experience feeling like my brain is rejuvenated and at peace. It is the exact opposite of every antidepressant I have tried, which have always been mentally and physically brutal starting, staying on, and coming off of.

I genuinely hope ketamine treatment becomes more accessible throughout the UK in the near future, especially seeing how many people around me have also been saved by it. If ketamine treatment did not exist or I did not have access to it as most people in the UK currently, I would currently be held in a psychiatric hospital against my will, as I have yet to find any other medication or treatment which is effective at controlling my illnesses.

Finally, another important aspect of ketamine treatment from my experience is working with a therapist or psychologist. My psychologist has helped track the changes throughout the treatment, while also helping approach my mental health issues from a non-medical perspective. While ketamine alone has helped reduce a

lot of my symptoms and the severity of the illnesses by providing the relief, the effect does wear off and is by no means a cure on its own.

THE USE OF KETAMINE FOR HEROIN WITHDRAWALL – MULITPLE NARRATIVES

When we reached out to the community to see whether anyone had experience of using ketamine for depression or addiction recovery, we did not find anyone that was using ketamine via the routes describes above, or using using ketamine for the treatment of depression illicitly. Our case studies above were recruited via the clinics providing the treatment, not the wider community. However, we received several (6 in total) accounts of the use of ketamine for heroin withdrawal, and we present here as a combined narrative to protect the identities of those who reported. All those that reported had not used ketamine specifically for withdrawal: it was an unexpected side effect. Additionally, all those that did use it returned to heroin due to either needing the money to live on through dealing, or being heavily involve in the community and not feeling ready to stop using. This highlights the importance of the psychosocial elements in supporting people to address their addiction.

'We were heavily involve dealing heroin and were waiting on a large score, but we unable to get any immediately. Someone turned up with a massive bag of ketamine, and although we hadn't had much experience of it, we dug in. 4 days later, and no bag of ketamine left, we came to our senses, and realised that none of us had any cravings for heroin! We had missed the pick-up, and we debated no bothering as we didn't feel the need. However, and this show how the psychosocial elements of addiction are more powerful than the physical aspects – we relied on dealing for money, and it was our community, so we soon returned to it.'

SUGGESTIONS FOR REFORM

1. WIDENING ACCESS

If racemic ketamine was approved by the Scottish Medicines consortium for TRD and substance use disorder (SUD) it could then could be added to the Scottish NHS Formularies so that GPs, consultants and regulatory bodies understood how racemic ketamine has been repurposed as an effective medicine for TRD and SUD. It may also form part of the MAT standards, as an alternative to current treatments.

However, as it stands Ketamine cannot be approved by the Scottish Medicines Consortium (SMC) due to it being a generic medicine (SMC, 2024)). The only way racemic ketamine, and all plant medicines such as psilocybin from the Scottish Liberty Cap, can be given approval from SMC is if the processes underpinning approval are updated to reflect modern (and traditional) healthcare treatments. This will involve close collaboration between Healthcare Improvement Scotland, the Scottish Government, and the communities involved in delivering and accessing these treatments.

Another option is to provide ketamine therapy as an option via the Medication Assisted Treatment (MAT) standards. Ketamine is a schedule 2, and therefore available to prescribe. We would suggest that in order to explore this option we look to develop a small project in which individuals are given the option of ketamine assisted therapy through the Eulas Clinic, and outcome are evaluated and measured against other treatments.

Going forward mechanisms of engaging HIS and other health bodies in both research and policy development is paramount, as they hold the key to smoother regulatory processes.

2. COST IMPLICATIONS

Costs is a barrier to small businesses setting up community based interventions. Allowing Eulas Clinic to support patients that have a treatment team and place, and to not require them to provide talking therapies if there is

a pre-existing care team in place, would greatly improve the health outcomes of patients that already know that ketamine treatment works for their disorder. Additionally, removing the requirement for retaining an anaesthetist would also greatly relieve the financial burden of setting up.

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