Ketamine in severe, highly treatment-resistant depression—a retrospective case study and a perspective

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Abstract

Ketamine is a well-known and widely available general anesthetic from the 1960s that, in sub-anesthetic doses, has been adopted in a limited manner for the treatment of acute suicidality and treatment-resistant depression. Its short onset time and short duration of action make it feasible for use at outpatient clinics. In the US, it has a long history of off-label use and was officially approved for depression treatment in 2019. In Finland, it has been administered to selected hospitalized patients in the public healthcare system since 2010 and became available at a private outpatient clinic very recently. In Norway, it has been administered off-label at a private clinic for approximately 500 patients since mid-2010s and at a public clinic for approximately 300 patients since 2020, with plans on opening more clinics in 2024. In the US, the treatment has been administered to hundreds of thousands of patients.

The retrospective ethnographic inquiry part of this study features a Finnish woman in her twenties who suffered from treatment-resistant depression, rooted in her insecure childhood and having been bullied at school, as well as income insecurity and excessive workload in adulthood. Eventually, she was violently raped, which induced an obvious post-traumatic stress disorder and exacerbated her depression, incapacitating her. In the course of approximately five years, she was prescribed ten different anti-depressive medications and seventeen other medications, including various antipsychotic medications and lithium. These failed to provide an anti-depressive effect but resulted in 'massive' adverse effects instead, including 60% weight gain and psychotic hallucinations. Eventually, esketamine spray treatment at a private outpatient clinic resolved her depression in a single session. A weekly re-administration process was ongoing.

In this case, repeated esketamine administration alleviated depression by producing accumulating corrective emotional experiences without the need to re-experience previous traumatizing events. In a few months to a year, the transient but accumulating anti-depressive effect typically leads to the resolution of depression in most cases, if the patients' living conditions no longer constantly re-traumatize them. It is necessary to adopt ketamine more widely as an emergency measure while more effective, non-addictive alternatives and complements are prepared for adoption. The cost of this specific pilot program implementation was unscalable, but costs can be reduced by approximately 90% by modifying the implementation details. Ketamine and its more effective alternative, 5-MeO-DMT, can serve a major role in facilitating a rebirth of public and private mental healthcare systems, with treatment efficacy multiplied and treatment costs simultaneously reduced.

Keywords: psychedelic therapy, psychedelics, depression, treatment-resistant depression, PTSD, C-PTSD, ketamine, psilocybin, LSD, MDMA, DMT, 5-MeO-DMT, reactivation

Introduction

In 2019, the OECD noted that Finland had the highest estimated incidence of mental disorders in the European Union (EU), with close to one in five being affected (Organisation for Economic Cooperation and Development (OECD), 2019). The economic cost, including the cost of treatment, social security programs, lower employment, and lost productivity, added up to an estimated 5.3% of GDP, approximately 15 billion Euros per year, or approximately 2800 Euros per capita per year. Finland ranked 9th on a list indicating the rates of depression in 180 countries, with 5.6% of the population, or over 300 000 people of the population of approximately 5.6 million, suffering from it (World Population Review, 2024).

In 2010, the head of the section of neuropsychiatry at the Turku University Central Hospital (TYKS), psychiatrist Tero Taiminen, introduced the treatment of hospitalized patients presenting with treatment-resistant depression and acute suicidality with sub-anesthetic doses of intravenous ketamine infusion in Finland (Naakka, 2023). However, access to this treatment, applied as a 'last resort' when everything else has failed, has been very limited.

Taiminen reviewed the history of ketamine and described in detail the treatment process at TYKS (Taiminen, 2017). The process involved a prescreening that included: a review of unconditional contraindications (pregnancy, lack of the use of contraceptives, schizophrenic psychosis, strong catatonic symptoms, hematouria of unknown cause, suspicion that the patient could not tolerate the return of depression after discontinuation of use); a review of conditional contraindications (somatic disease that could be exacerbated by ketamine, liver disease, history of drug abuse, increased

tendency for psychosis, catatonic features of depression); acquisition of informed consent from the patient; measurements of ECG, blood pressure, drug screen, and liver tests; estimation of the severity of depression with MÅDRS interview and BDI self-evaluation.

Treatment sessions involved a psychiatric nurse administering an infusion of physiological saline solution with 0.5 mg/kg of racemic ketamine for 40 minutes while monitoring blood pressure. After this, the patient was monitored in the hospital for at least four hours. If the patient exhibited a clear treatment response, reinfusions could be administered twice a week for the first two weeks. Usually, treatment sessions were administered once a week. If there was a clear response after three sessions, the treatment was continued for three months, for a total of 12–14 sessions. The duration or intervals could be adjusted individually. The initial laboratory tests were repeated monthly. Observed adverse effects could lead to the discontinuation of the treatment. In treatment processes lasting longer than three months, EEG, memory, neuropsychological, and a few other tests were delivered once a week. Some patients had been treated for up to 1.5 years, without notable adverse effects. After the end of the treatment, an obligatory waiting period of at least six months was required before considering another series of sessions.

Taiminen noted that two days after a single infusion, depression ratings showed 50% decline but after seven days, only 25% decline with respect to the baseline. However, the twice-a-week procedure led to a continuous decline of up to approximately two thirds from the baseline after two weeks. Possible long-term adverse effects remained unclear but possibly included risk of psychosis, cognitive decline, loss of treatment efficacy, induction of drug abuse, and psychological stress after discontinuation of the treatment. Taiminen stated that a more active treatment of depression was needed, and ketamine treatment should be applied more widely for both unipolar and bipolar depression as well as suicidality and concomitant pain.

Regardless, the police in the same city still complain that they are powerless in the face of having to deal with over five suicide candidates per day on average and 'cannot understand how these people cannot get treatment' (Rönkä, 2024). They often have to deal with the same person again in a few days, or even multiple times on the same day. An attempt to get one case admitted to the emergency room might take from one to several hours for a team of two policemen. The current state of psychiatric healthcare has been described as 'not about to collapse but already collapsed' (Rajamäki, 2023). Patients' mothers say that psychiatric hospitals only function as short-term storage facilities, leaving the patients' issues unchanged (Aalto, 2023a,b). Treatment guidelines are biased, reflecting only psychiatrists' interests, with other professions and viewpoints excluded from guideline committees Service (2023).

In January 2024, treatment with intranasal esketamine spray was made available at a private outpatient clinic in Helsinki, Finland. Two other clinics had either started a similar operation or were in the process of starting one.

In Norway, off-label administration of ketamine was initiated at a small district psychiatric outpatient clinic of the public Østfold Hospital in Moss municipality in the last quarter of 2020 (Blossom Analysis, 2023; Jakobsen and Spilde, 2023; Kvam et al., 2021). The price of a single dose is around EUR 4. The patients also pay a small, deductible consultation fee. Several private clinics in Oslo also offer the treatment for the price of EUR 400–700 per session, not including consultations before and after. The Norwegian Institute of Public Health (FHI) opposed approval of this indication, arguing that effectiveness and safety were not well documented, and waiting for 'more and better studies'. In February 2024, the first ketamine conference was organized in Norway (Sykehuset Innlandet and Sykehuset Østfold, 2024).

According to a US/Norwegian ketamine therapy pioneer, a regional director of private ketamine clinics, specialist emergency physician Lowan H. Stewart, Norwegian clinics utilized racemic ketamine either by infusion or intramuscular injection. Esketamine was not used due to its cost. A typical process consisted of four to six treatments over two to six weeks, costing about EUR 3 000. About a third of patients continued with once-monthly maintenance treatment from six months up to a few years, costing EUR 400–700 per month.

In the US, ketamine is commonly prescribed for self-treatment at home, with online video call consultations only (Hull et al., 2022). Stewart commented that the practice was relatively safe and worked fine, although not as well as infusions or injections for people who were really sick.

An in-between model was the combined outpatient clinic infusion and at-home self-therapy maintenance treatment with oral ketamine, currently carried out at the Oxford ketamine clinic, so that in between monthly infusions, patients were given oral ketamine to take if necessary (Oxford Health NHS Foundation Trust, 2022). In 2022, the cost of one infusion treatment session was GBP 225, and that of oral ketamine was GBP 60 per month.

According to Stewart, the Oxford model is the future of ketamine treatments. In Norway, this protocol is legal but had not yet been implemented due to pushback from the medical board and the psychiatric association, who were 'very worried about everybody becoming addicted to ketamine' or it becoming 'the new opioid epidemic'. Stewart attributed this to 'conservatism, fear, misunderstandings, misconceptions, and stigma about using a powerful psychoactive drug'. He pointed to a discrepancy between not being ready for ketamine yet and 'not having any problem with giving everybody amphetamines for ADHD'. The situation was changing, however: there were four active public ketamine units in Norway, and the practice was spreading, with more units opening in a year.

Ketamine is on the World Health Organisation (WHO) List of Essential Medicines, and it is the only psychedelic substance in the focus of clinical trials in Asia, especially in China (Wolswijk, 2023). Ketamine is available in two forms:

the traditional (R/S)-ketamine, i.e., racemic or generic ketamine, and the patented (S)-ketamine or esketamine (Spravato™). Due to its excessive cost, the esketamine product was not approved as a medicine in the UK and Canada (Wolswijk, 2023). The average annual drug costs were estimated at approximately CAD 300–800 for generic ketamine and CAD 19 000–46 000 for esketamine, an approximately 60-fold difference (Canadian Agency for Drugs and Technologies in Health, 2021). Also, a US study concluded that esketamine was unlikely to be cost-effective (Brendle et al., 2022).

Passie et al. found no significant differences between (S)-ketamine and (R/S)-ketamine in the reduction of psychopathological symptomatology or with respect to neurocognitive impairment (Passie et al., 2021). In addition, they found that (S)-ketamine produced somewhat more 'negatively experienced' effects, suggesting that the (R)-enantiomer might be associated with protective effects. They wrote that the antidepressant effect might depend on pleasantness and the absence of anxiety. Preclinical data also indicated that (R)-ketamine was more potent and longer-acting. Clinicians in both Finland and Norway have attempted to promote the use of the affordable (R/S)-ketamine over (S)-ketamine (Jakobsen and Spilde, 2023; Kantonen, 2023).

Codron, who suffered from suicidal depression, provided a patient's perspective in an online presentation (Codron, 2023). Before being admitted to an esketamine clinic, he self-medicated with street ketamine. The price of street ketamine was around EUR 12 per gram, while one 84 mg dose of esketamine cost approximately EUR 580. In his view, the dissociative nature of ketamine helped put things in perspective and balance again, and 'looking at yourself as a distant spectator could often help discover deeply rooted bad habits'. He commented that classical psychedelics, being non-addictive, were a safer alternative than (es)ketamine to provide big 'breakthroughs' with permanent outcomes. Similar 'aha-erlebnissen' were definitely possible with higher doses of ketamine, but the problem of addiction then loomed around the corner. Synergy could emerge from combining ketamine with classical psychedelics.

Palmer, who experimented rather comprehensively with most of the known psychedelics, noted that he recognized 'the enormous therapeutic potentials of ketamine in treating many serious conditions such as depression and addiction ... the effects of ketamine are often unparalleled ... ketamine is perhaps the most underrated synthetic psychedelic compound with perhaps the most potential value to humans' (Palmer, 2014). He did not, however, find it therapeutically useful for himself, and warned about the addiction potential of high doses in daily use.

Concerning safety of combinations, online harm reduction materials suggested that combining ketamine with common psychedelics and SSRIs had low risk with possible synergy Tripsit.me (2024). Caution was suggested with amphetamines, cocaine, benzodiazepines, and MAOIs. Combining ketamine with alcohol, GHB/GBL, opioids, or tramadol was dangerous. With regard to effects, Turner briefly described his early experiments about combining ketamine with other substances (Turner, 1994).

With regard to the history of ketamine for depression, in the 1990s, it was accidentally noticed that when patients were treated with ketamine for pain, their depression also dissipated (Taiminen, 2017). In 2000, Berman et al. published the first, very small, placebo-controlled, double-blinded trial that assessed the treatment effects of a single dose of ketamine in patients with depression, finding significant, over 50% decreases in the Hamilton Depression Rating Scale scores (Berman et al., 2000). In 2009, Mercer reviewed the use of ketamine in many of the major armed conflicts under difficult and stressful conditions, often with basic equipment and resources (Mercer, 2009).

In 2016, a book edited by Mathew and Zarate reviewed the first decade of progress of ketamine treatment for treatment-resistant depression (Mathew and Zarate, 2016; Stewart, 2018). The book covered the history, the basic and clinical pharmacology of ketamine, clinical studies, suicide risk, safety, tolerability, impact on neurocognition, preclinical and clinical evidence of mechanisms of rapid antidepressant action, comparisons with electroconvulsive therapy, and emerging data for ketamine in obsessive-compulsive, stress-related, and substance use disorders. The Multidisciplinary Association for Psychedelic Studies (MAPS) published another book that, in addition to therapy aspects, also included accounts of first person journeys, personal recollections, and discussions on ketamine dependence and how to make ketamine work in the long run (Wolfson and Hartelius, 2016).

In 2017, a Lancet article by Singh et. al. stated that ketamine use for severe, treatment-resistant depression did not violate ethical principles (Singh et al., 2017). Three primary ethical concerns included: the genuine need for treatment of patients with severe, treatment-resistant depression; the insufficient safety and efficacy data for off-label use of ketamine; and the misuse potential of ketamine. A key difference in clinical as opposed to recreational use of ketamine was the dose (several grams per day vs. milligrams) and frequency of use (daily vs. weekly or monthly). Less than daily use was not associated with the most serious side effect, i.e., ketamine-induced ulcerative cystitis ('ketamine bladder'); see (Misra, 2018). The balance of risk and benefit was such that new restrictions concerning off-label use (in the UK) were not needed. Singh et al. hoped that their recommendations enabled the innovative use of ketamine.

In 2019, the United States Food and Drug Administration (FDA) approved ketamine's enantiomeric compound, esketamine, for both treatment-resistant depression (TRD) as well as major depressive disorder (MDD) with suicidal ideation (Evans et al., 2023).

In 2020, a larger trial by McIntyre et al. found that patients with treatment-resistant depression and bipolar disorder presenting with prominent anxiety receiving intravenous ketamine exhibited a significant reduction in depressive, suicidal ideation, and anxiety symptoms (McIntyre et al., 2020). In 2020 and 2023, Kadriu et al. reviewed ketamine-related research, also comparing ketamine with classical psychedelics (Johnston et al., 2023; Kadriu et al., 2020).

A pilot study by Kheirabadi et al. (n=45) compared the rapid antidepressant and anti-suicidal effects of intramuscular ketamine, oral ketamine, and electroconvulsive therapy (ECT) in patients with major depressive disorder (Kheirabadi et al., 2020). They concluded that oral and intramuscular ketamine probably had an equal antidepressant effect and a better antisuicidal effect compared with ECT. Ketamine also induced fewer cognitive adverse effects and was preferred by patients.

In 2021, an article in Forbes magazine stated that ketamine-assisted therapy had gone mainstream (Yakowicz, 2021). This was because it was effective, legal, and short-acting. The best part of psychedelic therapies was that they gave patients hope. Just one chain of clinics was about to treat 65 000 patients in that year. A retrospective analysis on a naturalistic sample by O'Brien et al. found that a higher prevalence of childhood physical abuse correlated with a robust response to ketamine (O'Brien et al., 2021).

A Cochrane review by Dean et al. discussed ketamine and other glutamate receptor modulators for depression in adults with unipolar major depressive disorder, concluding that ketamine and esketamine may be more efficacious than placebo at 24 hours (Dean et al., 2021). In search of biomarkers for dissociation, Chamadia et al. found that ketamine was associated with structured electroencephalogram power and global coherence signatures (Chamadia et al., 2021).

The consensus view in the field of conventional biomedical psychiatry considers ECT to be currently the most effective therapy for depression. Ekholm et al. conducted a randomized, open-label, non-inferiority trial comparing racemic ketamine to electroconvulsive therapy (ECT) for unipolar depression (Ekstrand et al., 2021). They concluded that, despite being inferior to ECT, ketamine could be a safe and valuable tool in treating unipolar depression.

Veraart et al. reviewed pharmacological interactions, between ketamine and psychiatric medications used in the treatment of depression (Veraart et al., 2021). Benzodiazepines and probably lamotrigine reduced ketamine's treatment outcome. There was evidence for an interaction between ketamine and clozapine, haloperidol, and risperidone.

In 2022, Bowdle et al. noted that ketamine had psychedelic and analgesic effects; the historical labeling of ketamine as a 'dissociative' had been arbitrary and was not the best descriptor of its subjective effects (Bowdle et al., 2022). Hull et al. published findings from a large, prospective, open-label effectiveness trial (n=1247), indicating that at-home, sublingual ketamine telehealth was a safe and effective treatment for moderate to severe anxiety and depression (Hull et al., 2022). With respect to depression and anxiety, three patient subpopulations emerged, presenting either with improvement (79.3%), delayed improvement (9.3%), or no improvement (11.4%).

Lopez et al. stated that ketamine exerted its sustained antidepressant effects via cell-type-specific regulation of the Kcnq2 gene (Lopez et al., 2022). They suggested that this was a novel mechanism underlying the sustained antidepressant effects of ketamine. Adjunctive treatment with retigabine, a KCNQ activator, augmented ketamine's antidepressant-like effects. Yavi et al. provided another review of ketamine treatment for depression (Yavi et al., 2022).

VanderZwaag et al. reviewed the role of microglia in the therapeutic role of ketamine and psychedelics (VanderZwaag et al., 2022). They wrote that the role of microglia was largely under-investigated, and detailed sigma-1 receptors, serotonergic and γ-aminobutyric acid signaling, and tryptophan metabolism as pathways through which these agents modulated microglial phagocytic activity and inflammatory mediator release, inducing their therapeutic effects.

Carter et al. published a case report about intranasal esketamine for severe major depressive disorder with psychotic features (Carter et al., 2022). After two sessions within a week, her depression was reduced from severe to moderate. Over 14 sessions, she had no significant adverse effects, including no psychotic symptoms, and was stabilized to mild depression without suicidal ideation. One year after treatment, she continued to be stable, with an absence of auditory hallucinations since the first session.

A book chapter by Nikayina and Sanacora reviewed ketamine treatments, concluding that there was overwhelming evidence of the short-term clinical benefits of treatment with both ketamine and esketamine, but large, longer-term controlled studies examining the safety and efficacy of the treatment remained limited to esketamine intranasal treatment (Nikayina and Sanacora, 2022). A book by Siebert featured two descriptions of ketamine experiences and an overview of the therapy (Siebert, 2022). Pompili et al. presented three cases of esketamine treatment, resulting in a rapid reduction of depressive symptoms and a subsequent complete resolution of suicidal ideation and intent in the two patients with such risk (Pompili et al., 2022).

Focusing on esketamine, Borentain et al. commented on the Cochrane review by Dean et al. (Borentain et al., 2022). They concluded that esketamine improved response, remission, and depressive symptoms as early as 24 hours post-first dose among patients with TRD and among patients with MDD and active suicidal ideation with intent.

In 2023, Evans et al. presented a primer for primary care clinicians that reviewed relevant research and therapeutic applications (Evans et al., 2023). Lii et al. presented a preprint of a trial in which ketamine's acute psychoactive effects were masked by administering it under general anesthesia (Lii et al., 2023). Both ketamine and general anesthesia alone approximately halved the MÅDRS depression scores on day 1, and the outcome persisted through all follow-up time points up to day 14. Zaki et al. published interim results of a study about the long-term safety and maintenance of responses with esketamine, identifying no new safety signals (Zaki et al., 2023). Also, two patient-oriented books were published (Dow and Levy, 2023; Lassalle, 2023). A report by NBC News discussed the proliferation of ketamine clinics in the US (Dunn and Snow, 2023).

Arrighi et al. published a case report about long-term remission in a patient with severe and highly treatment-resistant depression, with no response to 14 different antidepressants and several neurostimulation techniques (Arrighi et al., 2023). Over 20 biweekly esketamine sessions, she had no significant adverse effects and was stabilized into remission. During the maintenance phase and a year later, she continued to be stable.

Singh et al. published an observational study (n=62) about the comparative effectiveness of intravenous ketamine and intranasal esketamine, concluding that the number of treatments required to achieve remission was significantly lower with intravenous ketamine compared to intranasal esketamine (Singh et al., 2023).

Assumedly the first case report on an adolescent, Skala et al. reported a case of a suicidal 17-year-old female with TRD treated with esketamine (28 mg, i.e., one third of a full dose) for seven weeks, resulting in modest gains in objective assessments but clinically insignificant improvements; the treatment was prematurely discontinued (Skala et al., 2023). It was unclear why Skala et al. chose to undermedicate.

Rayburn et al. noted that anyone with MDD remained at risk for suicide completion after several days from the last dose of esketamine, and precautions were necessary during and especially after treatment, even among those who admit no intent (Rayburn and Albright, 2023).

In 2024, Sumner et al. stated that ketamine's antidepressant properties were related to $GABA_A$ and AMPA receptors rather than the traditionally assumed NMDA receptor antagonism (Sumner et al., 2024). In a historical cohort study (n=52), Singh et al. suggested that patients with baseline suicidal ideation required more treatments to achieve a therapeutic response with ketamine or esketamine (Singh et al., 2024). Intravenous ketamine and intranasal esketamine did not differ in this aspect. Rawat et al. discussed the accumulation of the antidepressant effect, suggesting that it was associated with changes in bone morphogenetic protein signaling (Rawat et al., 2024).

In summary, several hypotheses related to the treatment's mechanisms of action from various perspectives and on various levels of abstraction have been presented. The research has focused predominantly on the brain, approaching the issue from the perspectives of molecular mechanisms, neuropharmacology, and bioelectromagnetism. The 'mechanism of action' thus remains undefined, but is irrelevant for clinical practice. The relevant aspects include safety, efficacy, and cost. Based on the above data, the safety of all administration methods may be considered adequate. Concerning efficacy and cost, intravenous or intramuscular administration of racemic ketamine was superior to esketamine administration.

Concerning the bioelectromagnetic approach to the treatment of depression, the most well-known method is electroconvulsive therapy (ECT) (Rojas et al., 2022). A frequent adverse effect of ECT is retrograde amnesia. Because of such concerns, ECT was not utilized in the present case. Another method for the treatment of depression is repeated transcranial magnetic stimulation (rTMS) (Saini et al., 2018). It is focused and bypasses the impedance of the skull and superficial tissues; these are considered advantages over ECT. The method involves the use of a small, battery-powered device with electrodes attached to the patient's forehead. A similar method, transcranial direct current stimulation (tDCS), utilizes low levels of electric current to stimulate the brain (Mutz et al., 2019). The latter method was utilized in the present case.

In general, psychiatry is plagued by excessive vagueness. What is actually being treated and how is often fundamentally unclear. Attempts to overcome this state of affairs often result in equally problematic, simplistic interpretations. For one, the concept of depression remains unclear. Various perspectives on depression have been proposed by, among others, Rantala and Luoto (2022), who suggested that depressive episodes could be classified into discrete subtypes that were induced by infection, long-term stress, loneliness, traumatic experience, hierarchy conflict, grief, romantic relationship dissolution, post-partum events, season, chemicals, somatic diseases, and starvation. Most of these aspects are typically ignored, leading to treatment failure. Treatment-resistant patients are typically affected by multiple of these causes simultaneously.

With regard to psychiatric diagnostics, typical diagnostic systems consist of consensus committee-devised pairs of labels associated with symptom sets (World Health Organization, 2010, 2024), where both the labels and the sets originate from a long history of subjective perspectives and opinions, meaning that they are rather arbitrary. At the clinic, self-reported and/or observed symptom sets are then matched with these predefined sets, resulting in a label, i.e., a 'diagnosis'.

Another set of predefined pairs controls the rest of the process: those associating diagnoses with medications. After a diagnostic label has been assigned, one of the corresponding medications is prescribed. As a whole, this chain of events, supplemented with various degrees of post-medication oversight, constitutes a 'treatment'.

TRD has been defined as a failure to respond to a varying number of different treatments with SSRIs, SNRIs, and other common pharmaceuticals with unspecified dosing and duration (McAllister-Williams, 2022). As the diagnosis of TRD depends on treatments, and treatments depend on a diagnosis of depression, TRD criteria appear not only vague but somewhat circular.

To complement this simplistic framework, perhaps originating from the treatment of viral infections, there exists the concept of 'psychotherapy', which is assumed to fill in the gaps; for example, take into account the life history and personal characteristics of the patient. Currently, this model rarely functions.

The details of the case have been acquired from two semi-structured retrospective online interviews with a total duration of 2.5 hours conducted in February–March 2024, as well as medical record excerpts and a written timeline of past prescriptions and diagnoses provided by the patient. Due to the excessive length of the medical record of this patient, only selected parts from the period between December 2018 and February 2024 were included in the analysis. A review of the manuscript was conducted afterwards. Additional details about ketamine treatments in Norway were acquired from a short online interview with Dr. Lowan H. Stewart.

Case description

A woman in her late twenties felt insecure during her childhood. Her family was middle-class, perhaps slightly below the average. Although both of her parents had jobs, they were emotionally unstable and suffering from chronic alcohol dependence. Her relationship with her mother was 'very difficult', and she felt emotionally abandoned. Around the age of six, she 'had to grow up, become an adult, be responsible for herself', as well as be responsible for handling—or suppressing—her emotions. Alone in her room, she had tried to handle her 'difficult emotions and depressive thoughts' on her own by keeping a diary. Her main strategy was to avoid or please aggressors (the 'fawn' reaction; see Walker (2013)).

In her family, 'showing any emotions was not the habit'. According to her medical record, her mother either criticized her or 'refused to talk to her for months'. Her parents hid their alcoholism from outsiders, but it 'felt very unsafe to live at home'. She was afraid of her parents when they were drunk. At night, she was afraid of the dark, afraid that someone would break into their house and kill them all. She suffered from insomnia. On many occasions, she stayed awake at night, monitoring her parents, who had passed out on the floor, and ensuring that they were still breathing. In retrospect, she considered that she 'had not received the required care'.

At the age of seven, she started comprehensive school. At the age of eleven, she overheard how her father planned suicide. Around the age of thirteen, her peers pressured her to use alcohol and tobacco, which she refused and became a target of bullying. She felt betrayed and abandoned by her best friend, who 'recruited the whole school into bullying and excluding her'. She described it as 'a very confusing period . . . I no longer knew myself. I could no longer kind of recognize myself'. She was diagnosed with mild depression and referred to a school social worker.

At the age of 16, as she moved to secondary school (i.e., gymnasium or preparatory high school), the bullying stopped. She felt relieved, and her situation improved. At the age of 19, she enrolled at a vocational university (polytechnic university), occasionally visiting a psychologist. She described the time as 'one of the best times of her life'. Around this time, her father quit drinking. Towards the end of the studies, she began stressing about the uncertainty of her future, becoming anxious. She had two short relationships, the latter of which ended suddenly 'for unknown reason'.

At the age of 22, she completed the vocational degree. For one and a half years, she worked as a solo entrepreneur in a relatively low-income business sector. Due to her low income, she took on two additional part-time jobs.

At the age of 23, the stress of juggling three precarious jobs, occasionally for 16 hours a day, led to burnout. She gave up entrepreneurship and, for the next few years, frequently changed jobs in the hope that a new job would improve things, each time ending up on sick leave, with her depression gradually deepening.

At the age of 24, an occupational health clinician diagnosed her with insomnia and mixed anxiety and depressive disorder (ICD-10 F41.2). She was initially described as 'generally in good condition but dispirited'. First, she was prescribed escitalopram, a selective serotonin reuptake inhibitor (SSRI) antidepressant. The clinician told her that escitalopram was for insomnia; she did not know that it was an antidepressant. She visited a psychologist a few times.

A month later, another psychiatrist diagnosed her with recurrent depressive disorder (ICD-10 F33), commenting that she 'did not seem severely depressed' but had social anxiety and, although she was 'beautiful with a normal body weight', had issues with her body image but no eating disorder. She was not close with her siblings. Her mother was still suffering from alcoholism. An intense period of experimenting with various pharmaceuticals was initiated. A four-month escitalopram experiment with an escalating dose scheme (10 mg, 15 mg, 20 mg) resulted in nausea but no improvement in mood. Instead, each dose escalation triggered a decline in her mood. Zolpidem (10 mg) and melatonin (3 mg) were prescribed for insomnia. She was diagnosed with recurrent depressive disorder, current episode moderate (F33.1) and nonorganic insomnia (F51.0). Her status had worsened. A decline in her mood and a notable increase in anxiety were considered a transient effect of the dose escalation of escitalopram, and her mood was expected to 'improve soon'. She was 'depressed, tearful, anxious, and hopeless', but not suicidal. She was given a week of sick leave.

After the sick leave, she was unable to show up at the workplace due to severe anxiety. She was diagnosed with recurrent depressive disorder, current episode moderate (F33.1) and agoraphobia (ICD-10 F40.0). Escitalopram was discontinued. A six-month period with duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant, immediately followed (30 mg, 60 mg, 90 mg, 120 mg), resulting in dizziness, sweating, and insomnia, but no mood improvement. A gradual de-escalation of dosing of duloxetine resulted in tachycardia, dizziness, and strong 'electric shocks' felt in the body. Alprazolam (0.25 mg), a benzodiazepine with a fast, potent tranquilizing effect of moderate duration, was prescribed for anxiety. It was later switched to oxazepam (15 mg), a short-to-intermediate-acting benzodiazepine. Doxylamine succinate (12.5 mg), an antihistamine, and mirtazapine (15 mg), an atypical tetracyclic antidepressant, were prescribed for insomnia.

At the age of 25, she was violently raped in her apartment by a man who choked her almost unconscious. The experience was about pain and fear of death. She dissociated and had an out-of-body experience. Afterwards, she felt like she had been on the edge of dying. She became afraid of her own apartment and moved away. She 'went into shock', tried to deny that the event ever happened, and never reported it to the police. According to a general practitioner, her latest employment contract was 'unexpectedly terminated'.

One month after the rape, she was granted a state allowance for twice-week cognitive-analytic psychotherapy for three years, with a diagnosis of mixed anxiety and depression disorder. For the following two years, she could not bring up the issue of rape during her psychotherapy sessions.

For the first time, she was diagnosed with severe unipolar depression by a general practitioner (ICD-10 F32.2: severe depressive episode without psychotic symptoms), with a BDI score of 33. She felt the loss of her job was her own fault and had suicidal thoughts and panic attacks. She was described as a perfectionist. Energy drinks were consumed daily. A three-month period with venlafaxine, another SNRI antidepressant, followed (37.5 mg, 75 mg, 150 mg, 225 mg, 300 mg). Dose escalations caused 'electric shocks', and the maximum dose caused 'really strong sweating', a hypomanic period of a month with 'an oddly artificial feeling of happiness', followed by a 'crash'. De-escalation again induced tachycardia, dizziness, and strong 'electric shocks'. Amitriptyline (10 mg, 25 mg), a tricyclic antidepressant, was prescribed for insomnia.

In her view, the hypomania was clearly an adverse effect of venlafaxine. She communicated that at a psychiatrist's appointment, but her view was dismissed. Instead, the psychiatrist diagnosed her with a suspected bipolar disorder (ICD-10 F31.8: other bipolar affective disorders). Her medical record claimed that she had chronic depression with mild suspected hypomania even before antidepressant use. Her response to SSRIs and SNRIs was poor. Lamotrigine was proposed as a primary medication, with doses between 50 mg and 400 mg. It was mentioned that it 'might also alleviate migraine'.

According to her, she had 'never presented with even a trace of bipolarity'. Notes from another psychiatrist indicated that she had been 'shocked' about the suspicion of bipolar disorder and stated that neither her neurologist nor her therapist agreed with the suggestion. There was no history of bipolar disorder in her family or extended family.

The predefined maximum of 300 days of sick day allowance was reached. She was granted rehabilitation allowance for one year (it had been continued, one year at a time, up to the time of the interview). Her friends could not understand her situation. Excessive sweating made her feel 'dirty' and avoid people. Gradually, she began alienating from people and what she referred to as 'normal life'; she felt she deviated from the norm too much.

She was prescribed lamotrigine (25 mg to 100 mg) for five months. She was informed that it was for the treatment of migraine; there was thus uncertainty about informed consent. Lamotrigine is typically used as a mood stabilizer in bipolar disorder, and a trial in 1997 indicated that lamotrigine is ineffective for migraine prophylaxis (Steiner et al., 1997). It was eventually discontinued because it induced eczema.

Another psychiatrist diagnosed her with recurrent depressive disorder, current episode severe without psychotic symptoms (ICD-10 F33.2). According to the medical record, her childhood was 'extremely traumatizing', she was 'clearly unable to work', and before hypomania induced by venlafaxine, she had never experienced similar symptoms.

A ten-month period with vortioxetine, another antidepressant, followed (5 mg, 10 mg, 15 mg, 20 mg). Initially, there was nausea, after which vortioxetine slightly improved her mood for a while. The slight antidepressive effect soon faded, despite dose escalation. In the first two months of this period, another significant adverse effect emerged either because of vortioxetine, other prescriptions, or their interactions. Her weight had been stable for years, with a body mass index (BMI) of 22.9 kg/m^2. In two months, her BMI increased to 36.6 kg/m^2, although according to her, neither her appetite nor eating habits had changed. She brought the issue up at the psychiatrist's appointment, but it was ignored without further comment. According to her medical record, a BMI of 33 kg/m^2 had been measured and labeled as 'normal'. She was afraid of discontinuing the medication by herself, considering it possibly dangerous. After discontinuation of vortioxetine, her BMI dropped to 31.6 kg/m^2, remaining at that level since.

Another psychiatrist diagnosed her with bipolar affective disorder, current episode mild or moderate depression (ICD-10 F31.31), and referred her to a public healthcare psychiatric outpatient clinic specializing in bipolar disorder. Quetiapine (25 mg), an atypical antipsychotic, was prescribed for insomnia; it caused severe day-time tiredness and 'brain fog'. Trazodone (50 mg), an antidepressant medication, was prescribed instead. Pregabalin (20 mg), an anticonvulsant, analgesic, and anxiolytic medication, was trialed for anxiety, but it caused 'brain fog', tiredness, and nausea. Subsequently, aripiprazole, an atypical antipsychotic, was also trialed; it induced akathisia and severe suicidal ideation.

As she was constantly either being introduced to a new medication and suffering from adverse effects or being phased out of a medication and suffering from withdrawal symptoms, her everyday life had little in common with those of her friends, who could not understand her situation. Her energy levels and moods were fluctuating, and as her insomnia was severe, she was often too tired or in too much pain to attend social events or function normally at them. Her social anxiety and alienation from social life constantly increased.

Due to not feeling heard or understood, she was switching from one private outpatient clinic psychiatrist to another, meeting perhaps nine different psychiatrists. The total number of visits covered by her private insurance was notable.

Two years after the rape, she mentioned something about the event to a friend who 'made her realize that it had been sexual abuse'. Before that, she had either tried to deny it ever happened or blamed herself for it. Subsequently, she also brought the issue up in psychotherapy; the therapist seemed to 'take it seriously'.

The referral to the psychiatric outpatient clinic had disappeared; she negotiated with the secretary of the clinic. Her diagnosis of severe unipolar depression did not qualify her to be treated at public psychiatric outpatient clinics but at community general practice clinics only.

At the age of 27, because of the suspected bipolar disorder, she was eventually enrolled at a psychiatric outpatient clinic. According to the medical record, she had 'one friend and a few online acquaintances'. She had suspected or mild Crohn's disease, migraine, allergies, hypertension, and a BMI of 33 kg/m^2, labeled as 'normal'. The ECG revealed inverted T waves. Her venlafaxine-induced hypomanic period was not considered to qualify as actual hypomania. A pharmacogenomic screen (Brown et al., 2022) revealed abnormal metabolism of at least escitalopram, citalopram, and atomoxetine. Her test scores included: BDI 39 (severe depression); Patient Health Questionnaire (PHQ-9) 22/27 (severe depression); Clinical Outcomes in Routine Evaluation (CORE-OM) 24.4; Overall Anxiety Severity and Impairment Scale (OASIS) 17/20; MÅDRS 29/60 (moderate depression); Generalized Anxiety Disorder 7 (GAD-7) 14/21 (moderate); Obsessional Compulsive Inventory Revised (OCI-R) 14/60; Epworth Sleepiness Scale (ESS) 16/24 (severe excessive daytime sleepiness); Insomnia Severity Index (ISI) 19/28 (clinical insomnia of moderate severity). Suicidal thoughts were transient, without an actual plan. She was diagnosed with severe depressive episode without psychotic symptoms (ICD-10 F32.2).

To her disappointment, the treatment was 'for the most part, only about forcing medication on me'. A three-week experiment with bupropion, an atypical antidepressant, resulted in strong, all-day fatigue and nausea and was discontinued. A three-month period with agomelatine (25 mg, 50 mg), another atypical antidepressant, resulted in slight fatigue with no other change. Sertraline (50 mg), a SSRI antidepressant, caused nausea and a severe decline in her mood and was discontinued after a month. Propranolol (10 mg), a beta blocker, was prescribed for anxiety.

During a five-month period with no medication, the state allowance for psychotherapy ran out, but her private insurance covered the costs for two more years, allowing her to continue it. In addition to depression, investigations at the psychiatric clinic revealed signs of post-traumatic stress disorder (PTSD), generalized anxiety disorder, panic disorder, and agoraphobia, but she was not officially diagnosed with these. In the medical record, it was mentioned that she 'had not felt heard' and 'had high expectations about various anti-depressive medications but was disappointed, eventually becoming desperate and hopeless'. She did not fulfill the criteria for bipolar disorder. There were no signs of psychotic features.

Once, she mentioned the rape to a psychiatric nurse, but it was ignored, and there were no further discussions about the issue. She never mentioned the rape to the psychiatrists because 'it would not have felt good' due to a lack of trust.

Moclobemide (300 mg), a reversible inhibitor of monoamine oxidase A, was prescribed. It effectively alleviated her anxiety but had no effect on depression; she experienced 'strong suicidal ideation' during this period. In the middle of this period, she was concurrently prescribed another SSRI, sertraline (50 mg), resulting in vomiting and strong nausea. She considered this prescription to have been malpractice.

Doxepin (1 mg), a tricyclic antidepressant, was prescribed for insomnia. Later, temazepam (20 mg), a benzodiazepine, was prescribed. Despite that, her insomnia became intolerable, with her 'not sleeping at all'. An earlier, concise nocturnal polygraphy in the public healthcare system had revealed mild obstructive sleep apnea. Private health insurance enabled her to attend a nighttime Level 1 polysomnography (PSG) in a private clinic. It revealed moderate sleep apnea, and she was prescribed a continuous positive airway pressure (CPAP) device, resulting in 'a change for the better' with respect to insomnia.

Regardless, severe depression remained, and around the middle of this period, her MÅDRS score was 32/60 and her BDI score was 40. There was a mention of her possible upcoming discharging from the psychiatric clinic due to being treatment-resistant. Her reality testing was intact, and she was not suicidal. With the coverage afforded by her private health insurance, she also trialed transcranial direct current stimulation (tDCS) for two months, five times a week for half an hour, feeling that it somewhat alleviated her depression. Her psychiatrist considered the decline in her BDI scores (from 49 to 40) insufficient and discontinued the treatment. She indicated interest in ketamine treatment and was referred to another psychiatrist for the planning of that method. An addition of sertraline (50 mg) was proposed but not started.

Moclobemide was discontinued and switched to duloxetine (30 mg, 60 mg), a SNRI antidepressant, for five months; the outcome was excessive sweating and another period of hypomania.

At the age of 29, two months before discontinuation of moclobemide, she was also prescribed lithium (300 mg, 900 mg) for four months, even though she opposed the idea and, excluding the hypomanic phases induced by venlafaxine and moclobemide, had not presented with bipolar symptoms. Eventually, she agreed to the treatment because she thought that 'there was no longer anything to lose'. Despite the serum lithium concentration being in the treatment range, lithium induced 'symptoms of poisoning': constant severe visual and auditory hallucinations, complete

insomnia, exacerbation of suicidal ideation, anxiety, and exhaustion—something that she described as a 'really bad situation'. Clothes hanged to dry appeared to her as dogs. Transient, delusionary visions emerged as confusing flashes. At night, she woke up, convinced that she was a shelf, and began organizing various items on the illusory shelf, i.e., on top of her body. Her field of vision was narrowed because peripheral vision was persistently either blurred or filled with 'a mass of shapes'.

Regardless of these adverse effects, the public health psychiatric clinic refused to discontinue the treatment. Instead, for some reason unclear to her, the psychiatrist wanted to increase her lithium dose. For her part, she did not know whether discontinuing the medication by herself would have been dangerous, and was accustomed to any changes in medication being carried out under the supervision of clinicians.

In any case, at this point, plagued by psychotic hallucinations and 'brain fog', she was too confused to think clearly and did not even fully realize the nature of her condition. Instead, her friend noticed it and essentially forced her to find another psychiatrist. Again, with the help of her private healthcare insurance, she was able to find a psychiatrist at a private outpatient clinic who agreed to cancel the lithium prescription. She characterized the lithium experiment as 'a total failure'.

For two months, she remained without antidepressive medication, but her depression worsened. With psychophysical physiotherapy, vocational therapy, antidepressants, and almost five years of psychotherapy traversed without much progress, she was 'on the verge of giving up completely'.

She did not want to attend electroconvulsive therapy (ECT) because she was afraid of the adverse effects: memory loss, learning difficulties, and an exacerbation of her chronic migraine. She applied for ketamine infusion treatment in the public healthcare system, but the application was denied due to her refusal of ECT. At the psychiatric clinic, she was treated by the same psychiatrist for most of the time, until the psychiatrist quit and she was referred to another one. She did not trust either one.

All in all, in approximately five years between the ages of 25 and 29, she was treated by more than ten different psychiatrists and was prescribed 26 different pharmaceuticals, including SSRIs, SNRIs, anxiolytics, antipsychotics, and lithium; a period she characterized as 'exceedingly difficult'. According to her, the medications and the depression had severely damaged her memory. The medication-induced periods of hypomania and the following crashes felt detrimental, complicating the situation. For the last four years, she was unable to work. She described being 'desperate' and failing to believe in 'any kind of future' for her. She did not attempt to commit suicide, but suicidal ideation was persistent, with plans to overdose on the medication.

According to her therapist, her depression had progressed to a near-catatonic state. Her MÅDRS score was 47/60. Eventually, a neurologist treating her for chronic migraine informed her about the possibility of esketamine spray treatment at a private clinic. Three months before the interview, she was enrolled in a pilot esketamine program at a private outpatient clinic. She was prescribed fluoxetine (10 mg) because concurrent medication with SSRIs was an obligatory condition to get special, personal permission for state reimbursement of esketamine from the Social Insurance Institution of Finland (Kela). After two weeks, it was granted. She paid for her esketamine prescription at a pharmacy, which delivered the medication to the private clinic.

Before the first session, her body was 'very tense'. With the nurse present, she lay down on the medical exam table and sprayed the medicine herself in her nose. The onset of the effect was rapid, and her body numbed. The experience was not scary, but the uncertainty of what was happening kept her slightly alarmed. Soon, a peaceful feeling descended on her. The first session involved her 'visiting a verdant park'. During that time, she was half awake, talking with the nurse.

The first session felt 'as if someone had turned on the lights in her brain'. Compared to the baseline, 'a completely different person walked out of the clinic'. The shift was 'radical—difficult to comprehend'. Her mood issues were resolved on the spot, resulting in happiness and love for life returning. Her ability to take initiative and function were restored. The change was so swift that after years of severe depression, it was 'difficult to adjust to feeling good'. Her post-session MÅDRS score was 6/60, down from 47/60.

Physically, during the sessions, her body numbed, often from the chest down. Sometimes her nose or mouth also numbed. She attributed this to the anesthetic effect and did not, for example, see a connection between numbing and the sensations during the episode of sexual violence, which were about pain and fear. In general, ketamine did not appear to cause traumatic events to surface. In fact, it had the opposite effect: it induced calmness and serenity and 'cleared up her mind': the constant stream of 'fearful, dark, chaotic, depressive thoughts' dissolved, replaced by a peaceful state of serenity, clarity, and happiness. Compared to the 'fully artificial' nature of venlafaxine-induced hypomania, the ketamine-induced state felt 'real, authentic', with a sensation of 'inner peace'. The newfound inner peace then allowed for everyday functioning.

Additional sessions were all similar, with calming 'hallucinations' of visiting pleasant locations such as sunny summer beaches and the simultaneous feeling of numbing in the body. Interestingly, each hallucinatory vision was connected to a specific color. On one occasion, she felt 'covered with feathers or cotton wool'. The calming visions were always imaginary, with the exception of one real memory from a few years ago, but that memory had also been about a moment of happiness. It was always clear to her that these 'hallucinations' were just mental images, not actual reality.

The role of the nurse consisted of writing down notes of what she talked about during the session. There were no questions or therapeutic interventions. She also listened to music during the session with headphones. Sessions were predominantly just 'relaxing', not tiring.

The initial sessions took three hours, but for the last few sessions, she had been able to reduce the process to two hours, with the last hour preparing to leave. Blood pressure was measured before and after the sessions. After a session, she often felt slightly dizzy. Just in case, she had an escort to make sure she got home after the session. At home, she typically felt tired and needed to rest for the remainder of the day. By the next morning, she felt normal.

At the time of the interview, she had attended ten esketamine treatment sessions in five weeks and was the first and only patient at the private outpatient clinic receiving the treatment. After nine sessions, fluoxetine was considered inconsequential and discontinued. The maximum duration of the ketamine treatment was planned to be between 9 and 12 months. Her current diagnoses were recurrent depressive disorder, currently in remission (ICD-10 F33.4) and nonorganic insomnia (ICD-10 F51.0).

A remaining issue was a fear of social interactions; it was difficult for her to meet friends or maintain interpersonal relationships. Also, ketamine had a slight negative effect on sleep; regardless, insomnia felt 'less of an issue than before the treatment', and did not incapacitate her.

The insurance coverage of her psychotherapy was ending, and she felt sorry about the sexual trauma remaining partly unresolved. She was sad that now, when she was more receptive and more capable of psychotherapeutic work, the resource had been used up and partly wasted. She considered therapy 'a big help' in supporting her, but because she had been 'in such a bad shape all the time', it had 'mostly been about extinguishing fires', i.e., about handling acute crises, often caused by the adverse effects of medications.

Before the start of ketamine treatment, she had been granted occupational therapy once a week, intended to help her with everyday tasks. Initially, the therapy consisted mostly of 'visualization-trance exercises'. After her ability to function had improved, it had changed into supporting interpersonal activities and everyday tasks. Remaining problematic issues included cooking and eating, which she tended to avoid. With regard to relationships, her mother had also quit drinking during the last few years, and her relationship with her parents had improved.

With regard to possible modifications to treatment practices, she did not consider group treatment suitable for her because of her social anxiety; previously, a group psychotherapy trial had failed. She commented that for some others, group sessions might be feasible. She did not consider the idea of ketamine sessions carried out unsupervised at home adequate. The idea of a nurse supervising a session at her home 'might be ok'; although she had never had any problems during a session, being at the outpatient clinic felt safer, 'just in case something might happen'. The feeling of safety was essential. She also mentioned that it might be interesting to combine the visualization-trance exercises of occupational therapy with a ketamine session.

She considered the conventional treatment practices she had been subjected to 'quite old-fashioned'. She did not understand why patients could not choose ketamine over ECT. In the interviews, she appeared normal, with no observable signs of depression.

Discussion

Some general observations could be derived from the above case description. Her childhood environment was unsupportive and damaging. The precarious nature of her working life exceeded her level of resilience. A medication later proven unsuitable for her by a pharmacogenomic screen increased her anxiety and deepened her depression. She became unable to show up at the workplace due to that. Other medications caused adverse effects that caused her to lose almost all of her friends. No one noticed that she was raped during treatment, or asked about such events. When she mentioned it to a nurse, she was ignored. Yet another adverse effect of medication was interpreted as a more severe psychiatric disorder. It was unclear whether there was an attempt to medicate that condition without informed consent. A sudden weight gain of 60% was ignored. Another antidepressive medication also induced suicidal ideation. She was pressured into the use of lithium for a reason unknown to her. It caused persistent psychotic hallucinations, the importance of which was downplayed, and dose escalation was recommended. As a direct result of medication, she began losing her reality checking ability and becoming immersed in psychotic delusions. She had no previous history of psychosis. Her medical record included no rationale for lithium treatment, but it was probably considered an augmentation strategy (Nuñez et al., 2022). A friend and private health insurance were needed to rescue the situation.

In this context, childhood trauma and adult-life sexual trauma faded in importance in comparison to the adverse effects of unsuccessful medication with 27 different pharmaceuticals. During the treatment, her health constantly deteriorated. Adverse effects were the predominant cause of her increasing social alienation. Recurrent disappointments deteriorated her trust in medicine and medical professionals. The efficacy of psychotherapy was insufficient, but its cost was enormous.

Excluding ketamine and additional resources provided by private health insurance, the described process is not untypical or extreme in the Finnish healthcare system. Instead of resolving pre-existing trauma, treatment often exacerbates it and accumulates new traumatic events directly caused by treatment. In this case, treatment appeared to not only accumulate emotional trauma but also exacerbate the symptoms that the medication was supposed to alleviate.

The case history might easily lead a reader to conclude that psychiatric clinics are dangerous places for patients. The responsibility for obvious harm and inefficacy resides effectively nowhere. As harm is the norm rather than the exception, it is considered normal, providing no ground for complaints. In the worst case, patients are blamed for it. In any case, patients rarely possess the resources or skill to neither recognize malpractice nor complain about it, as also illustrated by the present case.

Concerning current practices, the chief of forensic psychiatry at Niuvanniemi hospital, Markku Lähteenvuo, put it plainly in an interview in 2022, stating: 'It is plain stupid to try a similar medication for the third, the fourth, and the fifth time' (Ekholm, 2022). He added that patients have the right to demand effective treatment.

If treatments are planned to be given in some order and the patient refuses a specific treatment along this path, instead of hopping over that treatment, the whole process stops. Patients experience this as punishment. Due to her refusal of ECT, she was refused the ketamine infusion treatment and was essentially forced to remain ill. Despite the illusion of 'evidence-basedness', current practices result in negative treatment efficacy, i.e., harm, and negative net utility, i.e., burning money and wasting time for no purpose.

Clinicians implement an external committee-devised set of 'evidence-based recommendations' and are afraid of deviating from them because of uncertainty about the consequences. Fear stifles clinical innovation. Perhaps to ensure 'equal treatment', the enforcement of the same guidelines for all often results in a treatment adequate for no one. Some psychiatrists consider somatic causes out of the scope of psychiatry. Somatic clinics attribute all symptoms of psychiatric patients to psychiatric causes. Cases of endometriosis, bone fracture, cancer, and pulmonary embolism have been dismissed and left undiagnosed and untreated because of that.

In the field of cybersecurity, there is a concept of 'security theatre' that refers to procedures that 'provide the feeling of improved security while doing little or nothing to achieve it' (Schneier, 2003). Most of the current psychiatric treatment practices could be considered 'psychiatric care theatre': a lot of dabbling around with no substance. In addition to an enormous financial cost, the unnecessary delay in implementing ketamine treatments has produced a lost generation of TRD patients.

The problem of overcompliance

Even in the face of severe adverse effects such as persistent psychotic hallucinations, the patient did not cease self-administering the medication responsible for these effects. It is difficult to predict what would have happened if she had not had friends or private insurance allowing her to obtain a second opinion.

The problem of overcompliance appears to be at least fourfold. First, an unrealistic belief in the competence of authority figures is very common: patients cannot believe that a clinician or a psychiatrist could be wrong. Typically, such a belief would endanger their basic emotional security or take away their last hope for improvement. Second, patients may consider self-initiated discontinuation of medication possibly dangerous and are afraid of doing it by themselves; they may not know the basic principles and properties of psychiatric medications or even what their medications actually are for. They are thus unable to make informed decisions. Third, although the law grants patients the right to self-determination (The Finnish Parliament, 2024), many medical professionals react very negatively to the non-compliance of psychiatric patients, resulting in often subconscious negative attitudes or other punitive consequences towards the patient. Fourth, almost all chronic patients depend on sick pay or rehabilitation allowances controlled by psychiatrist-issued medical certificates, and losing the allowances would cause them financial ruin. The resulting fear keeps them from making independent decisions.

Economic considerations

The pilot program treatment costs

In 2024, in Finland, there was an annual maximum limit of approximately EUR 630 on out-of-pocket reimbursable medicine costs for the patient. After the maximum was reached, each additional prescription of a reimbursable medicine cost the patient EUR 2.50 only.

As the price of one full dose of esketamine (84 mg) approximately matched the annual maximum, the annual cost for a patient undergoing the described kind of treatment process was approximately EUR 800 (1 x 630 + 51 x 2.50), and for the state, around EUR 30 000 (4 weeks x 2 x 200 + 48 weeks x 600 - 800).

The clinic fee for a session with a nurse was approximately EUR 300 per session, resulting in an annual total of around EUR 17 000 (4 weeks x 2 x 300 + 48 weeks x 300). For her, these costs were covered by her private health insurance package, which was purchased by her parents when she was a baby. Without it, she would have been unable to attend the treatment.

In summary, the approximate annual costs were EUR 800 for the patient, EUR 30 000 for the state, and EUR 17 000 for the private insurance company; in total, approximately EUR 48 000. The psychiatrist's appointments were not included in the calculation. From the perspective of cost efficiency, the main factor was the cost of esketamine. As discussed, choosing it over generic ketamine is clearly unsustainable. Also, the level of supervision might be excessive.

Comparison to the Oxford model

In the Oxford model, infusion sessions were not individual but in shared rooms with several patients, supervised by one nurse (Oxford Health NHS Foundation Trust, 2022). The cost of one infusion treatment was approximately EUR 300 per session, and the cost of oral ketamine was EUR 80 per month. With this model, an initial period with four to six infusions at an outpatient clinic over two to six weeks would cost about EUR 1200–1800, and a month of maintenance would cost EUR 380, giving an annual total cost around EUR 6 000.

Compared to this esketamine pilot implementation, an implementation resembling the Oxford model should be approximately 90% cheaper and thus scalable and sustainable on a population level, as the cost of no treatment or treatment with the current practices is the same or higher. Instead of a clinical setting, ketamine group sessions could be organized along the lines of psychedelic group session practices (Turkia, 2022d). One potential extra-medical context for such groups could be the church.

With regard to prescreening and regulatory considerations, a situation involving a suicidal patient unable to get adequate care should be paralleled with a battlefield situation. If healthcare facilities are overloaded or unwilling to adopt new treatments and the police are overwhelmed with suicidal people, ketamine treatment could be organized by the police by hiring an on-call clinician or nurse to administer intramuscular or intranasal racemic ketamine either on the spot or at the police station, with the nurse left to supervise the patient until the session is completed. Later, if needed, the patient could call the police nurse directly.

Even one such on-call nurse might suffice to resolve the issue city-wide. The financial cost would be equal to the nurse's wage, and the arrangement would result in significant savings as well as an improvement in job satisfaction in the police force. It is essential to ensure that the patient feels safe and comfortable in the chosen environment, i.e., that the person supervising the session is able to 'hold space' for the patient (see, e.g., Turkia (2023a)).

The economic burden versus treatment costs

In 2022, Taipale et al. identified 15 405 people from nationwide registers diagnosed with TRD in Finland during 2004–2016, and matched them one-to-one with comparison persons with depression who initiated antidepressant use but did not have TRD at the time of matching (Taipale et al., 2022). They compared healthcare utilization, costs, and productivity losses between TRD patients and the comparisons. The annual economic burden for TRD patients was EUR 16 000 versus EUR 8 000 for the comparisons.

The annual economic burden of such a TRD group as a whole would thus be around EUR 250 million, and the one-time treatment cost would be around EUR 100 million. Assuming that the economic burden of a non-depressed person would be zero, a response rate of 50% would reduce the burden to EUR 125 million. The cost of treatment would thus be covered in one year, and for the following years, the burden would be halved.

If these treatment costs are considered too high, they can be lowered to zero by decriminalizing or legalizing self-treatment with psilocybin mushrooms and other classical psychedelics, with the treatment self-organized along the lines described in these case studies (Turkia, 2022b,c, 2023b). Assuming that 10% of patients with MDD or TRD would self-organize and respond to such treatment, a 10% reduction in the economic burden could be achieved for free. Psilocybin-containing plants are not controlled under the 1971 United Nations Convention on Psychotropic Substances (Schaepe, 2001a,b). Since they are under domestic law, adopting the presented kind of self-treatment would be straightforward. Currently, according to a precedent issued by the Supreme Court of Finland in 2017, psilocybin is considered comparable to cannabis (Supreme Court of Finland, 2017).

Rodgers et al. investigated why low-cost ketamine remained inaccessible to patients in need in Australia (Gilbert, 2023; Rodgers et al., 2023). As there was no commercial gain for pharmaceutical companies in supporting a listing of off-patent ketamine as a treatment for depression, it was not listed by the national regulatory authority for such use and thus could not attract state funding for the treatment. For two decades, public funding to support research and patient access had been slow, uncoordinated, and underfunded. The costs of session supervision were prohibitive to most. They concluded that there was 'an urgent need for structural reforms'.

Many aspects of these counterproductive practices remain difficult to understand. There is no actual need for additional studies on ketamine for TRD. The constant demand for ever more research appears to be driven by the fear of uncertainty and the unwillingness to take action and learn by doing. However, 'action is the magic word'. The addiction to an illusion of safety is typically a symptom of complex trauma, which in this case is society-wide. The procrastination or unwillingness to act may be another symptom: a 'freeze' reaction.

Regulatory authorities could simply list off-patent pharmaceuticals for the necessary indications by themselves, without the need to involve pharmaceutical companies. More broadly, we could question the overall need for regulation based on an unserviceable patenting system whose effect has appeared to be net negative.

Not everyone is in need of supervision, or it can be arranged on a case-by-case basis outside the medical context. The absolute requirement that patients need to be monitored by a medical professional for hours after administration should be reconsidered in the context that suicidal patients are left on their own for months or years in any case. The suicidality of individual patients may only reflect the suicidality of society as a whole ('Humanity as a whole is like lemmings going off a cliff' (Rowland, 2024)).

Complements and alternatives

Clinical applicability of ketamine versus classical psychedelics

Comparing the clinical applicability, classical psychedelics, including psilocybin and LSD, are somatically safe, i.e., in practice, they cannot be lethally overdosed and do not induce an addiction (Turkia, 2022c). In the clinical context, they have proved difficult to adopt for the following reasons: they are not legal or available in most locations; their duration of action varies from several hours in the case of psilocybin to a day in the case of LSD; they often produce visions that clinicians are rarely able to understand and interpret; clinicians don't have prolonged or any personal experience of their effects. Due to these reasons, classical psychedelics have mostly been applied in self-treatment (Turkia, 2022b,c), often in psycholytic (i.e., low or 'half') doses. Alternatively, they have been successfully used in one-day or multi-day non-clinical group contexts (Turkia, 2022d).

An effective healthcare system should not adopt tasks that can be handled elsewhere. Ideally, every citizen should be able to heal themselves independently, without any external contributions. The current system rarely incentivizes this goal. Instead, it advertises the need for specialists and experts for nearly any purpose or indication, yet often fails to produce the advertised outcome or even the service itself. There is thus an obvious case and an immense need for a population-wide introduction of self-treatment practices. For this purpose, classical psychedelics may be superior to oral ketamine.

Concerning clinical use, ketamine appears superior: it is legal, established, and has a short duration of action. These characteristics make it practical for clinicians working at conventional clinics. Although ketamine may induce psychedelic effects, they are not as central to the process as with classical psychedelics. The clinician thus does not necessarily need to have similar personal experience with the substance or advanced skills in interpreting psychedelic visions.

With regard to the hesitation about the use of classical psychedelics in public healthcare, it could be noted that ketamine is also a psychedelic, although short-acting (Bowdle et al., 2022). It has already been clinically used for the treatment of TRD for decades, although in psycholytic doses, without issues.

Although this patient experienced mild effects, higher doses may produce a typical psychedelic experience of a death-rebirth cycle. Stafford et al. provided a description of one experience that started with disorientation and visions: the world and the body disappearing, feeling horror, experiencing death, surrendering or yielding to it, entering a space without words, experiencing Buddha nature or oneness with the universe, feeling 'at home' in a state of unforeseen bliss, wanting to stay there, then re-emerging back from the experience (Stafford and Bigwood, 1992). The facilitator of this experience commented that 'what happened and happens to others is that you finally get rid of that heartbreak feeling that we carry from childhood. Finally, that's expunged somehow'. The patient agreed: 'That was the feeling: I was rid of my heartbreak. My heart was no longer broken. It was like, Whew!!! That was the long-lasting effect—what really lasts and gets supported by similar experiences—not necessarily on any drug at all. That floats and stays'. As with classical psychedelics, this kind of experience is likely to produce a more efficacious and permanent treatment outcome.

According to Shulgin, another major difference between classical psychedelics and ketamine is that in high doses, ketamine may induce true hallucinations, defined as 'an extremely rare phenomenon, in which a completely convincing reality surrounds a person, with his eyes open, a reality that he alone can experience and interact with' (Shulgin and Shulgin, 1997).

Comparing ketamine to MDMA, which is not a classical psychedelic but an 'empathogen', their acute effects differ, so that MDMA typically induces a euphoric state, while ketamine induces a more 'neutral', serene state with a clear mind. The MDMA-induced state might resemble hypomanic states, often with a sudden drop to the baseline or below it, unless a gradually decreasing dosing scheme is used. Post-session, the state may seem to have an 'artificial' nature to it. Regardless, MDMA treatment is often productive, with permanent results; two other case studies describe its use in alcohol addiction and occupational stress release (Turkia, 2022a, 2023a). In treatment-resistant conditions, it is usually necessary to combine MDMA with LSD (Turkia, 2023c).

Cases of severe trauma may be treatment-resistant to classical psychedelics. Anecdotally, ketamine may transcend such resistance, subsequently allowing treatment with classical psychedelics. Further research on this aspect is warranted. Also, in order to release trauma-related tension encoded in the autonomous nervous system and the fascia (Oschman, 2006), the administration method and the environment should be such that the patient's body can freely move without the risk of injury. For example, the patient could be administered either intramuscular or intranasal racemic ketamine and then lay on a large mattress on the floor. With respect to the treatment of C-PTSD, with the currently utilized low dosing, ketamine appeared to function in the same cumulative manner as classical psychedelics, resolving complex trauma gradually over a relatively long time.

Alternatives to ketamine

Psychedelics with similar efficacy and clinical feasibility appear to be rare; in fact, there may be only one obvious candidate for an alternative to ketamine. In his book published in 2018, Oroc presented the Oroc Entheogen Scale, an order of preference for various psychedelic substances (Oroc, 2018). Substances were listed in order of increasing toxicity and decreasing capacity to induce experiences of oneness. The substances are thus listed in order of their safety and

the magnitude of their effect, the latter of which, to a degree, corresponds with therapeutic efficacy, but does not equal it. Oroc noted that the scale 'naturally descended by the chemical class of the compound—tryptamine, phenethylamine, opiates, amphetamines, alcohol—and that this corresponded to a noticeable increase in toxicity'.

The first two substances on the list are endogenous tryptamines; that is, they occur naturally in the human body as well as in many animals and plants. They thus exist in the sphere of animals, or more specifically, in the sphere of mammals. Some other psychedelics, such as psilocybin, occur in mushrooms but not in animals. In Oroc's view, endogenous tryptamines had a central role in spontaneous altered states of consciousness, and as such, they were a fundamental aspect of being human.

The second item on the list is DMT (N,N-dimethyltryptamine). While it also has a short duration of action and intensive effects, its effects are typically hypervisual, with the induced visions being difficult to interpret. It is typically considered more suitable for the study of the mind than therapy.

The first item on the list is 5-MeO-DMT (5-methoxy-N,N-dimethyltryptamine, often colloquially called *bufo*), a less-known psychedelic with clinically feasible characteristics similar to ketamine. It is typically considered to represent the ultimate in efficacy in psychedelic therapy. In order to get perspective on its purposes in the body, it may be related to the 'white light' often reported in the context of near-death experiences. Figuratively, it could be assumed that it might prepare a person for 'life after death': eternal bliss. Since a treatment session with 5-MeO-DMT would produce the effect already before death, the outcome would essentially be 'Heaven on Earth', similar to the ketamine-induced death-rebirth cycle described above.

Oroc considered 5-MeO-DMT the least toxic of all psychedelic substances. Considering that it is an endogenous molecule, that would be logical. It is, however, also the strongest of the known psychedelic substances. From the point of view of cost-efficacy, it is superior and thus the obvious choice in the current situation, when, in order to end wars and manage the consequences of climate change, the societal goal must be a full, population-wide eradication of transgenerational complex trauma.

For the treatment of 'deep trauma', i.e., very severe or early complex post-traumatic stress disorder, sexual trauma, or war trauma, classical psychedelics often appear lacking. Slowly and gradually, they resolve a lot but not all; they essentially fail to go deep enough, at least with the conventional dosing (e.g., up to 600 µg of LSD). They are too slow in many cases, with the process taking several years. For this purpose, 5-MeO-DMT is likely superior to all others.

The rest of the items on Oroc's list relevant for this study were: LSD, psilocybin, ketamine, mescaline, 2C-B and 2C-I, THC, MDA, and MDMA, with the last two crossing the 'fatal overdose line'. With respect to patients who are treatment-resistant to classical psychedelics, 5-MeO-DMT likely possesses the same capacity as ketamine to transcend this resistance. 5-MeO-DMT is also likely superior to possible patentable alternatives to classical psychedelics or ketamine in development. Its cost would likely be comparable to racemic ketamine, i.e., irrelevant.

With regard to formal scientific research on 5-MeO-DMT, the majority of it has been conducted after 2010. Shen et al. reviewed the metabolism, pharmacokinetics, drug interactions, and pharmacological actions of 5-MeO-DMT (Shen et al., 2010). Szabo et al. wrote that dimethyltryptamines could act as systemic endogenous regulators of inflammation and immune homeostasis through the Sigma-1 receptor (Szabo et al., 2014). Davis et al. stated that 5-MeO-DMT used in a naturalistic group setting was associated with unintended improvements in depression and anxiety (Davis et al., 2019); the main subjective features were 'spiritual experience' and 'blissful state'. An observational study (n=42) by Uthaug et al. indicated that a single 5-MeO-DMT session in a naturalistic setting was related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrease in psychopathological symptoms (Uthaug, 2020; Uthaug et al., 2019). Ermakova et al. presented a narrative review on the history, pharmacology, pharmacokinetics, effects, drug interactions, and toxicology of 5-MeO-DMT (Ermakova et al., 2021). Reckweg et al. presented a phase 1 dose-ranging study to assess the safety and psychoactive effects of a vaporized 5-MeO-DMT formulation in healthy volunteers (Reckweg et al., 2021). Ragnhildstveit et al. presented a longitudinal case study of a patient who successfully self-medicated her PTSD with 5-MeO-DMT (Ragnhildstveit et al., 2023). Concerning DMT, Timmermann et al. found 'a striking similarity between DMT-induced near-death experiences and actual near-death experiences (NDEs) (Timmermann et al., 2018). Dean et al. showed in a rat model that the mammalian brain endogenously synthesizes DMT (Dean et al., 2019).

A significant overdose of 5-MeO-DMT might induce respiratory failure (Oroc, 2009); however, such doses would be neither necessary nor therapeutic. Adverse interactions could occur with MAOIs, lithium, benzodiazepines, some SSRIs, and tricyclic antidepressants (Ermakova et al., 2021). This might limit clinical use in psychiatric patients, but ketamine could be used at the beginning of the treatment process instead. 5-MeO-DMT may induce 'reactivations', a perhaps unique property of 5-MeO-DMT. In a 'reactivation', the treatment process continues after the pharmacological effect has already subsided. A reactivation can be triggered by low doses of classical psychedelics. It may also may rarely occur spontaneously (Dourron et al., 2023). Regardless, the reactivation phenomenon can be utilized to extend and intensify treatment, so that a session with classical psychedelics can 'replay' features of the more effective 5-MeO-DMT session, but with lower intensity and for a longer duration. Thus, a 5-MeO-DMT session, augmented with a psycholytic session of LSD (e.g., 50 µg) a few days later, may produce an optimal combination treatment in which the psycholytic 'replay' session functions as a 'psychedelic integration' session for the more intense 5-MeO-DMT session.

When extended in this manner, reactivations cease to occur. Reactivations might thus be best understood as a delayed release of accumulated trauma. These therapeutic possibilities warrant additional study.

A recent case study by the author demonstrated the efficacy of 5-MeO-DMT (Turkia, 2024). It featured a woman in her mid-thirties who witnessed her mother's violent suicide and its aftermath at the age of three. Before and after that, her childhood was characterized by domestic violence and sexual abuse perpetrated by several members of her family and extended family. In her twenties and thirties, she became involved with the local mafia with the intention of asking them to kill her father, who had been the main perpetrator of the sexual abuse and violence. This plan was eventually not carried out, but it reflected her deep bitterness and wrath.

A two-year process initiated in her early thirties involving four 5-MeO-DMT sessions and a few additional sessions with psilocybin and ayahuasca completely resolved her symptoms related to the abuse, to the extent that she could rebuild a functional relationship with her father and feel love and compassion towards him. This outcome, i.e., the complete reversal of her attitude and emotions towards her father, appeared highly unusual. For the last three years, the outcome had remained stable.

In 2023, Reckweg et al. presented the results of a phase 1/2 trial to assess the safety and efficacy of a vaporized 5-MeO-DMT formulation in patients with TRD, with the efficacy measured as the proportion of patients in remission (MÅDRS $\leq$ 10) (Reckweg et al., 2023).

In the phase 1 part with eight patients investigating the safety of a single dose of either 12 mg or 18 mg, two out of four (50%) of patients administered 12 mg, and one out of four (25%) administered 18 mg were in remission at day 7. The mean MÅDRS change from baseline to day 7 was -21.0 (-65%) and -12.5 (-40%) for the 12 and 18 mg groups, respectively.

In the phase 2 part, eight different patients were administered up to three increasing doses of 6 mg, 12 mg, or 18 mg within a single day, using an individualized dosing regimen. Seven out of eight patients (87.5%) achieved remission at day 7 ($p < 0.0001$). All remissions were observed from day 1, with 60% of remissions observed from 2 h. The mean MÅDRS change from baseline to day 7 was -24.4 (-76%).

Reckweg et al. concluded that the treatment was well tolerated and provided potent and ultra-rapid antidepressant effects. Individualized dosing with up to three doses on a single day was superior to single dose administration. In 2024, another phase 1 clinical trial was ongoing in the US (NCT05698095) (Usona Institute, 2023).

5-MeO-DMT administration could be significantly less frequent than ketamine administration, and the number of sessions could be significantly lower. If necessary, treatment processes could be initiated with ketamine and continued with 5-MeO-DMT. This would likely allow most of the cases currently estimated to be 'hopeless' to become relatively easily treatable. This would likely also open completely new perspectives on what is possible for societies and for humanity as a whole. In summary, 'treatment-resistant depression' only means 'current treatments-resistant depression'. Concerning cost-efficacy, compared to current practices, with 5-MeO-DMT, a 100-fold improvement might be realistic.

Conclusions

In the described case, intranasal esketamine spray treatment at an outpatient clinic was clinically feasible and effective in the immediate resolution of treatment-resistant depression, at least in the short term. The treatment represented an immense improvement over the preceding practices. A widespread adoption of racemic ketamine treatment is necessary as an emergency measure. Ketamine and its more effective alternative, 5-MeO-DMT, can serve a major role in facilitating a rebirth of public and private mental healthcare systems, with treatment efficacy multiplied and treatment costs simultaneously reduced to a fraction. Additional delay in the adoption of these methods is unethical from the perspective of patients and self-destructive from the perspective of society.

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Abbreviations: The following abbreviations are used in this manuscript:

5-MeO-DMT	5-methoxy-N,N-dimethyltryptamine
BDI	Beck Depression Index
C-PTSD	complex post-traumatic stress disorder
DMT	N,N-dimethyltryptamine
ECT	electroconvulsive therapy
EEG	electroencephalogram
GABA	γ-aminobutyric acid
GDP	gross domestic product
Kela	Social Insurance Institution of Finland, or Kansaneläkelaitos
LSD	lysergic acid diethylamide
MDD	major depressive disorder
MDMA	3,4-methylenedioxymethamphetamine
MÅDRS	Montgomery–Åsberg Depression Rating Scale
PTSD	post-traumatic stress disorder
rTMS	repetitive transcranial magnetic stimulation
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
tDCS	transcranial direct current stimulation
TRD	treatment-resistant depression

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