Ketamine - The Fast Lane Out of Depression?

Survey of a psychoactive substance between market pressure and recreational pleasure.

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The brain is a huge, diverse chemical factory.
John Lilly.

Introduction.

We are living in strange times. The chemical factory mentioned above has become a battleground, where a diverse ecosystem of agents are working on extending their field of influence, masked by scientific integrity and medical benevolence. That under the sterile white surface political and economical interests are virulent driving forces has been highlighted by numerous critical voices in the tradition of Michel Foucault and Richard Sennett. Also to be briefly mentioned here is Latour's book titled Laboratory Life, which examines how in the field of science, the epitome of a de-emotionalised and objective domain, insisting to legitimise the trust invested by society, informal social dynamics remain as a sort of unruly contamination with disturbing effects. This paper intends to examine the rather remarkable history of a psychoactive substance, Ketamine, which, as has had a reputation recreational drug, and is now in the process of being reabsorbed by the pharmaceutical complex as a promising agent for TRD. The promotion of the substance goes hand in hand with the creation and inflation of the corresponding problem, and so the shift in attention, the change in language, in the course of which a certain dramatisation in regards to a certain disorder takes place, needs to be taken into consideration.

TRD: from residual phenomenon to category disorder.

What exactly is therapy resistant depression? Depression, a clear cut medical category, is a unipolar affective disorder as defined in national and international diagnostic manuals. Its lifetime prevalence is estimated 20-26% and 8-12% in women and men respectively. WHO estimates a total of 350 million people currently suffering depression.

Treatment algorithms commence with a single antidepressant agent. Increasing the dosage, shifting to alternative types of antidepressants follow up if the patient does not respond. Further augmentation strategies involve adding a second agent, which can include lithium, atypical antipsychotics or thyroid hormone,

pindolol, buspirone, dopamine agonists.[1] On the next level, if no remission has been achieved so far, somatic therapies such as ECT or rTMS are administered. Whereas this cascade of measures can be understood as a kind of trial-and-error approach, it represents a consistently psychopharmacological approach to depression. Uncertainties and unpredictabilities regarding to the response of the patient are objectified, summarised as external factors. The label TRD, treatment resistant depression, is issued relatively early in the process: Not responding to the first lineup of antidepressant already suggests the presence of TRD, with the differential diagnosis of Pseudo-TRD. Pseudo-TRD is deemed to result from patient non-compliance, somatic causes such as hypothyroidism or "latent bipolarity".

Following estimations, 10%-30% of the patients in treatment do not show signs of improvement in the wake of an antidepressant treatment. As a consequence, patents are categorised, rather early in the process of exploring the possibilities of treatment, under the label TRD. The term TRD in turn receives its significance due to its high prevalence combined with the grave connotation of the wording. Initially a term, which was installed as a marker for a residual phenomenon, is thus compounded to a pseudo-disorder.

The next day promise.

The current standard in treating depression focuses on biochemical interventions on the synaptic cleft by means of serotonins reuptake inhibitors. The substance is administered orally, on a daily basis. The effect of which is a gradual change in the levels of neurotransmitters, which is understood to alleviate depressive symptoms. The drugs are expected to unfold the desired effect after 4-6 weeks after commencing the treatment. Whereas this is acceptable in the case of a chronic depression, the clinical picture of which involves symptoms present over a longer period of time, other more acute cases, which involve the treatment of patients at acute risk of suicide, are driving the demand for substances, which promise a rapid effect. Implicitly, the promise of an instant cure is transposed to the chronic cases. This demand is corroborated by the widespread prevalence of depression in the population, expressed by economical figures such as the loss in productivity. The website of the ketamine advocacy group presents a 1,300 Billion Dollar loss due to depression, bipolar, PTSD and anxiety on a global level[2]. Thus, time is money, as much for the individual, who might be put out of work due to decreased functioning, as much as for society as a whole. Stakeholders are presented pressuring data. In this light, any means that promises instant remedy have to be taken into consideration.

In 2004, the US National Institute for Mental Health, has launched a clinical trial with the purpose to examine whether "Ketamine can cause a rapid-next day antidepressant effect in patients with Major Depression/Bipolar Disorder"[3]. The trial is in phase 1, and expected to present results in April 2017. At the same time, a series of private clinics are currently offering Ketamine injection treatment for depression and

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3363299/#b77-ppa-6-369

[2] http://www.ketamineadvocacynetwork.org

[3] https://clinicaltrials.gov/ct2/show/NCT00088699

chronic pain. These commercial clinics are advertising the procedure as the next miracle for cases, where all hopes are seemingly lost.

Whereas scientific studies exalt the rapid effect of intravenous Ketamine treatments, with alleviating effects setting in within hours after administration, the question arises as to how sustainable a treatment of depressive symptoms through the use of a dissociative hallucinogenic substance can be. Are we expected to encounter another class of population, permanently sedated and tripping, with hardly any exit strategy at hand? Is this another episode of driving out the devil with the Belzebub, as Freud has formulated his remorse in treating a morphine addict with cocaine?

The hype has entered the media, the taboos around the substance have eroded over the last years. The article titled " Ketamine: A Miracle Drug for Depression, or Not?", on the website of everyday health.com, sums up the turn the substance is bound to take in public perception. "Ketamine is best known as an illicit, psychedelic club drug. Often referred to as "Special K" or a "horse tranquilizer" by the media, it has been around since the 1960s and is a staple anesthetic in emergency rooms and burn centers. In the last 10 years, studies have shown that it can reverse — sometimes within hours or even minutes — the kind of severe, suicidal depression that traditional antidepressants can't treat." [4]

There are first attempts to answer the question. Coming out of the closet, Vice magazine has posted a self report of an individual, who has actually ventured to undergo a Ketamine treatment in a private clinic. The subject, with a history of experimental recreational drug use, delivers his ambivalent testimony:

"With the IV (intravenous) treatment, you start disassociating with everything, like you're observing, not participating in anything. It's really weird. I don't know how to explain it. As far as the mind goes, you start going through these weird levels, kind of like Inception or The Matrix, where you don't know what's real. You start thinking about all kinds of stuff. Whatever races through your mind—and usually when you're depressed it's negative shit—when you're on ketamine it's just like, Well, nothing I can do about that. You feel like, I'm not in control, and that's fine; you're going to die someday and that's just life. You kind of learn to just accept it, I guess."

What starts out like a bearable state of mind, even though all motoric activity is suspended for the time of the drug effect, is then put into perspective after the effect of the drug has subsided: "The next day, I'm just depressed and a day after that, I'm back to normal. So that kind of sucks."

Yet the periodic treatment could bring improvements to the quality of life: "You've got to get successive treatments, though. With some people it takes two; with some people it takes ten. But it helps. After my first treatment, I felt good for a week. Not the kind of bipolar 'good' where I'd be manic. I just felt pleasant, and not crazy or compulsive. I felt normal for the first time in a long time. But this was the first treatment, a low

[4] http://www.everydayhealth.com/columns/therese-borchard-sanity-break/ketamine-miracle-drug-depression/

dose, and it kind of wears off. It's not like you crash or anything. During the next treatment, they boost up the level that you're given, so it would start working successively, staggering. After that, I started feeling better."[5]

Remarkable is also the insight stated by the test subject regarding a combined therapy approach: "You'd think they'd have some therapy to go along with the ketamine. The way I experienced it, sometimes it felt like you could go either way, like you could have a bad trip. But it did help. Once it got to a point where I could afford it, I started going to a psychiatrist and a therapist once a week. So that combined, I'm definitely in a way better place than I was."

The psychodynamics of the drug, marked by rapid onset of effect followed by a harsh decline without apparent symptoms of withdrawal is paralleled by a supposed emergent capacity to allow for long term remission. This though can not be directly derived from the psychokinetic effect of the substance. Ketamine "trips" are reported to be rather short term, lasting from 30 minutes to a maximum of two hours, depending on means of administration.[6] Can it be that the cognitive state, which the patients repeatedly achieve in the course of the IV treatment series allows for a change in the cognitive structure?

The following four findings, cited from Serafini et al.[7], The Role of Ketamine in Treatment-Resistant Depression: A Systematic Review, are in line with the testimony above, further indicating the substance effect, which can be interpreted as a rapid improvement of the subject's attitude towards his own biography, suggesting a change in the perception of one owns circumstances beyond a mere hallucinatory experience.

Mathew et al.[8] reported that, in a sample of twenty-six medication-free patients, 65% of patients met response criterion (50% reduction from baseline on the MADRS) after 24 hours of ketamine infusion. Specifically, 54% of patients met response criterion 72 hours after ketamine.

In another study, Ibrahim et al.[9] reported that forty-two TRD patients significantly improved in MADRS scores from baseline after a single intravenous infusion of ketamine (0.5 mg/kg) with initially large and throughout the 28-day study moderate effect sizes of improvement. It has been showed that the mean time to relapse was 13.2 days whereas 27% of ketamine responders had not relapsed by 4 weeks after a single ketamine infusion.

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[5] http://www.vice.com/read/i-used-ketamine-to-treat-my-depression-122

[6] https://erowid.org/chemicals/ketamine/ketamine_faq.shtml

[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4243034/

[8] Mathew SJ, Murrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression a pilot randomized, placebo-controlled continuation trial. Int. J. Neuropsychopharmacol. 2010;13:71–82.

[9] Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, Moaddel R, Wainer I, Luckenbaugh DA, Manji HK, Zarate CA. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology. 2012;37:1526–1533.

Shiroma et al.[10] reported that 91.6% achieved response criterion and 66.6% remitted in a sample of fourteen subjects with TRD intravenous ketamine (.5 mg/kg) over 40 minutes during a 12-day period. After the first infusion, only three and one subjects responded and remitted, respectively. The authors suggested that 28.6% patients achieved response and 42.8% remitted after three or more infusions whereas 35.7% subjects experienced a prolonged remission during the 4 weeks of follow-up. Also, the mean time for 42.8% of subjects who relapsed was 16 days.

Murrough and colleagues[11] also conducted a prospective open-label study in a sample of 24 TRD individuals who underwent a washout of antidepressant medications followed by up to six infusions of ketamine (.5 mg/kg) three times weekly over a 12-day period. After 2 hours of treatment, a persistent mean reduction in MADRS scores has been reported and the overall response rate was 70.8%. Response at 4 hours was a significant predictor of response at study end and the median time to relapse after the last ketamine infusion was 18 days.

The Ketamine experience: a life-changer?

The predominant effect of Ketamine is on NMDA receptors (non-competitive antagonist) with a series of other subsidiary effects as weak agonist of the μ-opioid and κ-opioid receptors (10- and 20-fold less affinity relative to NMDAR, respectively), very weak agonist of the δ-opioid receptor, agonist of the D2 receptor, and inhibitor of the reuptake of serotonin, dopamine, and norepinephrine.

Yet additionally to its effects on neurotransmitter metabolism, Ketamine is observed to have effects on stimulating neuroplastic activity. “In the executive hub at the front of the brain — or prefrontal cortex — of rats, they discovered that a low dose of ketamine rapidly activates an enzyme, called the mammalian target of rapamycin (mTOR), that makes proteins forming the connections between neurons, or synapses.”[12] Whereas the findings are used in the study to fuel the promise of finding the next prodigal drug in the treatment of depression, “important and novel strategy for the rational design of fast-acting antidepressants”, the reported substance induced neuronal growth, “single dose of ketamine boosted levels of synapse-associated proteins within 2 hours and increased the number of neuronal ‘spines’ — or budding synapses — within 24 hours”, the reported rewiring of the synaptic apparatus is calling for a correlation of the bespoken neurogenesis with changes in the ego-structure as reported by recreational users.

In the context of recreational use, reports citing cosmic unity and out of body experiences are quite frequent. These phenomena, at times concomitant with a incapacitation of sensory perception, hint to a possible

[10] Shiroma PR, Johns B, Kuskowski M, Wels J, Thuras P, Albott CS, Lim KO. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. J. Affect. Disord. 2013

[11] Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol. Psychiatry . 013b; 74:250–256.

[12] mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists . Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. Science. 2010 Aug 20;329(5994):959-64.PMID: 20724638

“reconfiguration event”. A sort of shift in perspective, in which the subject experiences distance to its everyday life takes place, one seems to become the observer in the same way as one steps out of his vehicle, and enjoys watching as it is running through the carwash. The following samples are excerpts from randomly chosen self reports as found on the erowid.org website. Interestingly enough, from the three obtained samples, each one contained at least one instance, where a supposed “re-programming” could be evidenced.

“All sensory perception disappeared, in what must have only been seconds after I had dropped the syringe. The drug now forcefully turned off everything that was me, my entire consciousness shut down. From there it rebooted my consciousness, but when it booted back up it wasn’t me, it was an empty shell of a consciousness, a blank ego. It was like the drug was reformatting my brain for a new person. One by one traits, qualities, and memories of another ego were being uploaded into the empty shell that my brain was running. After awhile enough of this information had been uploaded to constitute a person. (…) The drug had seemed to defragment(ize) my ego much like a computer would defrag itself. I felt like I ran much better and more efficiently then I used too.”[13]

“I had experienced the dissociation of identity before with insufflated dose but this time it was different, this time it took minutes to get to that peak but in a different level and intensity, it was as if I merged with the everything and I was part of all around me, there were no divisions, unable to move but experiencing oneness with everything. (…) After a few minutes I wasn't there anymore, I felt a sudden rush, but not a physical rush the kind I have with XTC or LSD but more of a consciousness rush, it was as if I suddenly entered the quantum field of the wholeness interconnected and downloaded a hell lot of information that was being channeled straight to my being (…) I could see my ego identity from outside and identify it for what it is, and I could see every aspect of myself that I knew was holding me back, but from an external, objective point of view. The most acknowledging feeling of every aspect of myself and how it affected me in each level of my life.”[14]

“As I lay on my back, swept away by the profundity of the experience of being so close to death, all my cares, worries, and insecurities melted away, and there was nothing, nothing in the whole universe, but simply being, being in this state of pure existence; the utter, elegant simplicity of existing purely as a soul filled me completely and I felt absolute peace. I dwelled upon that euphoric sensation for a long time, simply being grateful for my existence and for being able to transcend everything, to get to this point where there was nothing but absolute peace. The colors and gentle sounds of the kaleidoscope played upon my closed eyelids. (…) As I listened, it seemed that every song contained an answer that unfolded itself for me. I watched as a pattern of circles came together and formed a number: 36. (At the time, this seemed to be relevant to a situation I had dealt with in a fitting room earlier that day, trying on different sizes of bras to find the one which fit best; ultimately, none of those which I tried on had fit very well and left me feeling unsure of my true size.) Other answers settled quietly into my subconscious; certainly they are still there.”[15]

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[13] “Ego Rebooted, Reformated, and Defragmented”, reported by Tycone, https://erowid.org/experiences/exp.php?ID=79954

[14] “Cosmic Orgasm”, reported by M.G., https://erowid.org/experiences/exp.php?ID=62998

[15] “Absolute Peace”, reported by H.Love, https://erowid.org/experiences/exp.php?ID=91431

Conclusions.

Comparing the reports, one is struck by the consistency of the material in regard to what could be called ego-plasticity. The experiences in conjunction with Ketamine can be differentiated from hallucinations in general in a sense that the experiences center on the self. It seems that past biographical events are revisited from a different perspective, and one is reminded of Ebenezer Scrooge's delirious journey through his immediate environment on Christmas Eve. It is exactly this bird's eye perspective journey which allows him, Scrooge, to reevaluate his own ego structure as the consequences of his mean attitude are revealed to him.

The reporters seem to draw pleasure from this flow motion, anxiety seems to be absent, as are supernatural ideations typical for LSD experiences. It seems that there is a temporary regression to narcissistic states, in which super-ego functions are suspended. If depression is understood to be triggered by the presence of violent super ego objects, one would need to take the reported experienced fantasy of defragmentation as a hint to a loosening up of the grip of these objects. If the reporter struggles with threatening and persecutory impulses, such as being "unsure of my true size", it seems that the substance allows for the import of unconscious parts of the super-ego onto the domain of the conscious. Whereas the regression into the safe haven of the narcissistic stage allows for a closer contact with the libidinal resources associated with the Id kernel, the ego now appears to step aside for a moment, allowing for a more unmediated exchange between Id and super-ego. It seems that the role of the ego turns from being a wretched negotiator to an observer, which now removed of responsibilities is allowed to watch internal safeguards being exposed to an uninhibited flow of childlike energy as "worries and insecurities melt away". The effects of the substance are concentrated on the mechanics of secondary elaboration. Where as significant biographical facts are present, the preconscious domain is explored, items are ushered into consciousness without experiencing distortion, the story lines by which they are held together through past products of secondary elaboration, appear to be rewritten in relief.

Yet the question remains if the evidence underpinning structural change in the synaptic connection in the cortical regions can be correlated with a corrective overwriting of secondary elaborations, hinting towards changes in the psychic apparatus to be of a sustainable quality. If one understands the formation of self perception in the state of a regression to the depressive position, to take place under the influence of aggressive currents impeding on the writing process, leading to self denigrating narratives, depression itself coming to being as the accumulation of bad narrative objects, it seems that understanding the effect of Ketamine as an antidepressant catalyst could be better approximated by adopting a psychodynamic perspective taking the hypothesis of a libido infused secondary elaboration as a tentative model of departure.