KETAMINE, COVID & SUICIDALITY – A PERFECT FIT FOR A PERFECT STORM

Alan Howard

WHY KETAMINE?

Molly.

Molly *(not her real name)* was a 50-something frequent flyer in our Emergency Department in the North West of Ireland. A habitual self-harmer and polypharmacy overdoser, she was the quintessential treatment resistant depressive with co-existing Axis II issues. The psychiatry unit had all but washed their hands of her, and all those involved in her frequent care simply went through the motions, presentation after presentation, month after month. I lost count of the sutures I had placed in her self-inflicted wounds and would have recognised her by her glottis, so often had she been tubed in our ED. That she lived literally minutes from our Emergency Department had undoubtedly played a role in the longevity of this troubled soul.

"Molly is on her way in again," remarked one of my registrars on a busy Thursday afternoon. "Sounds quite serious." It was.

PARAMEDICS HAD BEEN CALLED TO MOLLY'S HOUSE AFTER YET ANOTHER FLARE-UP OF LETHAL SUICIDAL INTENT. IN FRONT OF THEM SHE GRABBED A KITCHEN KNIFE AND SLIT HER OWN THROAT. SLIT, AS IN EXPOSED HER STERNOMASTOIDS AND ALL BUT TRANSECTED HER LARGE VESSELS.

Having miraculously dissected around any vital structures, Molly's latent surgical skill had spared her a visit to theatre or the afterlife. I elected to repair the damage in layers in the Emergency Department and reached for my go-to procedural sedative, ketamine. A few boluses were required during the 30-minute procedure. As I secured a Yeat's drain and waited for Molly to come around while a bed was found in the psych unit, I wondered when a successful attempt would eventually end the destructive cycle that was her life. I arranged for her to come back for a follow up and moved on to an unstable DKA.

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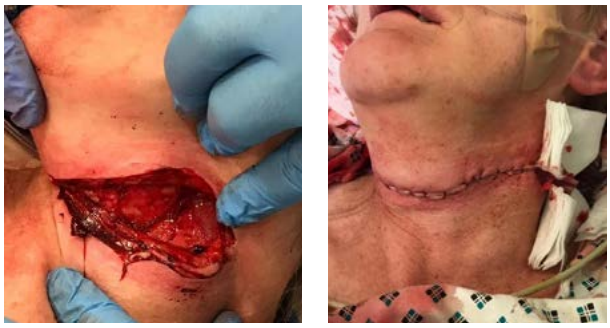
A week later and I had all but forgotten about Molly until notified by the clerk that she had arrived. Were it not for the neat Mepore dressing on her neck, I would not have recognised her. She had metamorphosed from an unkempt, withdrawn, and pitiful human being to an engaging, presentable and, dare I say, cheerful lady. And no, she is not bipolar.

"I feel great!" she remarked, while I scanned her notes for the miracle drug that had hitherto evaded the attention of the entire psychiatry department. There was none. Just the same old monoaminergic and mood-stabiliser combo staring back at me like a well-used recipe for pancakes in a dogeared cookbook. Molly shook her newly coiffured head and laughed. I realised it was the ketamine.



Molly's attempted suicide – before and after repair of her self-inflicted neck laceration under ketamine. A week later, all suicidal ideation had disappeared, and her demeanour had changed dramatically. (With permission)

In truth, I had read about the effect of ketamine on mood and, come to think of it, had even recognised unexplained and dramatic changes in demeanour

in patients I knew to be depressed (even suicidal) who had serendipitously received ketamine as procedural sedation for unrelated conditions as diverse as dislocated shoulders and ankles. (I use a *lot* of ketamine as an Emergency Physician).

Quite coincidentally, shortly after Molly (who was not seen again in the Emergency Department for about four months, when she presented with a cracked rib), I was lent *The Ketamine Papers* by a registrar with an interest in psychedelics. I researched and read anything I could find about ketamine and mood disorders and was intrigued by the successes of Steven Mandel (an anaesthetist) at his Ketamine Clinics of Los Angeles. (To date, his clinic has administered over 9500 infusions).

After 20 years abroad as an Emergency Physician (12 of which were spent at the same Emergency Department in Ireland working blocks of a few months at a time interspersed with visits back to the Natal Midlands), I decided to call it a day and return home.

I tested the waters by approaching a few psychiatrists I knew and administering ketamine infusions (with the requisite monitoring and emergency backup) a la the Los Angeles model. The response, demand and outcomes exceeded expectation. Ketamine Clinics of South Africa (KCSA) was born and I bade farewell to the Emerald Isle and Molly for good (See article which follows).

MADDOX, STEVENS, AND SOME PRISONERS.

CI-395 was synthesised by Harold Maddox in Detroit Michigan in 1956. Renamed phencyclidine, marketed by Parke-Davis as Sernyl and abused on the street as PCP or Angel Dust, CI-395 was rapidly consigned to the pile of 'really bad ideas', much to the relief of men in blue across the USA. Users went completely bananas. Disorientated, manic and violent behaviour coupled with immunity to pain, were the hallmark effects.

In 1962, Prof Calvin Stevens tinkered with CI-395 and came up with a somewhat milder analogue, CI-581. Ketamine had been discovered. Two years later, unsuspecting prisoners in Maddox's old stomping ground, Michigan, 'volunteered' to try the stuff with some gentle persuasion from a Dr Domino. The results were pleasing. Anaesthesia was achieved, the prisoners were all quite manageable and, curiously, they reported weird out of body experiences and believed their limbs had become detached. Henceforth, ketamine became labelled a 'dissociative' anaesthetic, a term coined by Dr Domino's wife.

In the 1960s treatment and understanding of depression was firmly focussed on the monoaminergic theory with iproniazid having been synthesised the decade before. Had Stevens, Domino et al only known that they had stumbled across the first glutamatergic antidepressant half a century ahead of time, how differently might history have unfolded. Perhaps they noticed that the prisoners were unusually cheerful for a few weeks.

ACRONYMS, MORE ACRONYMS, AND THE VIETNAM WAR

In 1966 the **USPTO** (United States Patent and Trademark Office) awarded a patent for ketamine as a dissociative anaesthetic in humans. In 1970 the **FDA** (Food and Drug Administration) approved ketamine for use in all ages. In 1985 the **WHO** (World Health Orgainsation) added ketamine to their list of essential medicines. During the early 70s, Ketalar™ was the most widely used analgesic and anaesthetic agent on the battlefields and in the field hospitals of the Vietnam War. In 1999, the **DEA** (Drug Enforcement Administration) classified ketamine a Schedule III controlled substance citing only 'moderate or low physical dependence potential' with 'less potential for abuse than substances in Schedules I & II'. Nobody from these eras recognised the antidepressant potential of ketamine.

RATS, MICE AND FINALLY SOME PATIENTS

In the early 90s, with the help of some despairing rodents, Trullas and Skolnick first demonstrated the major role played by the NMDA receptor complex in antidepressant action.[1]

Berman et al first studied the antidepressant effect of ketamine in human subjects with MDD and published their findings in 2000.[2]

It took a further six-years for Carlos Zarate's seminal randomized trial of ketamine in treatment-resistant major depression[3] to get the ball rolling, and it has been gathering momentum ever since.

Numerous trials have been conducted to date studying response to either a single ketamine infusion or series of infusions. 'Response' is deemed as at least a 50% reduction in depressive symptoms as determined using mostly HAM-D or MADRS scales. The effect of ketamine on reducing suicidal ideation specifically has also been the subject of several randomized controlled trials and 'significant reduction' is universally reported (approaching 80%).

The most remarkable finding has been the rapidity with which ketamine usually reduces or reverses suicidal ideation (within hours). This feature has enormous implications as a 'safety net' while longer term treatment and therapy is planned and implemented - not to mention avoiding costly hospitalisation.

A review of all the literature available at time of printing (2016) is systematically presented in Professor Sanjay Mathew and Carlos Zarate's excellent book *Ketamine for Treatment-Resistant Depression, The First Decade of Progress.*[4]

"REVERSAL OF SUICIDAL IDEATION IS OBSERVED IN 70-80% OF PATIENTS WITHIN HOURS AFTER A SINGLE KETAMINE INFUSION."

IF THE ONLY TOOL IN YOUR BOX IS A HAMMER, EVERYTHING STARTS LOOKING LIKE A NAIL

For 40 years or more, the hammers in the treatment of depression have been monoaminergic antidepressants. There have been various iterations of this hammer over time, and hammering has worked for several patients. There has been little else. Now there is a new target – the glutamatergic receptors.

One evening, a few months back, I settled down to read chapter one of *The NMDA Receptors*, edited by an eminent Japanese scientist. I still understand extraordinarily little about NMDA receptors, (so complex is the subject), but can strongly recommend the book as an alternative to zolpidem.

In a nutshell, ketamine is primarily a non-competitive antagonist of the NMDA receptor. Its effect is to increase levels of the amino acid glutamate, the major excitatory neurotransmitter in the central nervous system. Modulated by the inhibitory neurotransmitter GABA (of which glutamate is, curiously, a precursor), glutamatergic neurotransmission has dramatic and rapid effects on normal and pathological mood and behaviour.

There are several types of glutamatergic receptors each of which serves a unique purpose within the brain. It is postulated that the glutamate burst caused by ketamine stimulates AMPA receptors leading to increased expression of BDNF and consequently neuroplasticity and synaptogenesis. Interestingly, there is also evidence from more than one study that it may in fact be the R-enantiomer of ketamine producing most of ketamine's antidepressant effect and, in particular a sustained effect. *(See comments about esketamine later)*.

It matters less how it works and more that it works. While the science is fascinating, the profound effect that I have seen on patients' lives is even more so. Ketamine has been dubbed 'chemical ECT' (without detrimental cognitive effects). I prefer to think of it as 'limbic liberation'. A breaking and reset of the destructive loop between the elements of the limbic system that fuels and escalates depression to the point of suicide.

WHO SHOULD ADMINISTER KETAMINE?

Shortly after I launched KCSA in August 2019, a colleague remarked: *"What's an Emergency Physician doing administering an anaesthetic to psychiatry patients?"*

A perfectly reasonable question and one worthy of careful consideration given the blend of disciplines involved. I have since had a discussion with a psychiatrist who believed only they were qualified to administer the drug as an antidepressant, and yet another conversation with an anaesthetist who felt exactly the same (from the perspective of her profession).

This quandary raises two especially important issues: appropriate patient selection and safe administration of an anaesthetic agent. The first relies on accurate diagnosis of MDD and suicidality or bipolar disorder and careful exclusion of schizophrenic patients or those who are manic or hypomanic. The second, equally if not more important, recognises that ketamine is an anaesthetic and, notwithstanding an impeccable safety record due largely to a self-maintained airway and intact gag reflex, airway (and other) emergencies can and do arise. The ability to recognise and deal with such emergencies is, in my view, non-negotiable when administering ketamine (by any route). Therefore, even intranasal esketamine (Spravato™) is administered in a hospital setting in the US.

"KETAMINE REMAINS AN ANAESTHETIC AGENT. THE ABILITY TO RECOGNISE AND MANAGE EMERGENCIES IS PARAMOUNT."

In our Irish Emergency Department, we would not permit registrars to administer ketamine for procedural sedation unless they had attended a recognised sedation course and had advanced airway management skills. In South African practice the attitude is somewhat more gung-ho, and interns and community service doctors administer large doses of ketamine with impunity and little oversight. That there are not more adverse events speaks to the safety of the drug and in no way justifies any misguided sense of invincibility felt by the inexperienced junior doctor administering it.

It is worth mentioning that ketamine via the intramuscular route (used at times for acute trauma when vascular access is not immediately achievable) is no safer than intravenous ketamine. Absorption can be unpredictable, and any adverse effects cannot be curtailed by 'switching-off the infusion'.

THE LEFT HAND DOESN'T KNOW WHAT THE RIGHT IS DOING, OR DOES IT?

Ketamine is cheap.

Call me cynical, but this is why ketamine infusion, despite a wealth of evidence, is not yet mainstream therapy for treatment resistant depression and, in particular, suicidality. The racemic (50:50) mixture of the left and right mirror-image enantiomers (like a left and right hand), cannot be monetised for use in resistant mood disorders or KNAI (ketamine for non-anaesthetic indications). The patent has long since expired, along with Maddox, Stevens, Domino *et al.* To boot, ketamine is on the WHO list of 50 essential medicines with all of the associated financial implications and constraints on pricing.

Enter Spravato nasal spray. Realising that ketamine actually works for depression, Janssen in a chemical sleight of hand, isolated the left-enantiomer of racemic ketamine, esketamine, and were successful in patenting this and achieving FDA registration for use in resistant depression. Squirting it up the nose might hint at a possible outpatient utility but, no, it still has to be given under controlled clinical conditions – and, obviously, it costs a bomb. (A nuclear bomb).

Spravato costs, on average, $750.00 per treatment (two squirts) in the US. The recommended regimen

of 8-treatments in the first month followed by one every other week translates to an annual cost of $24,000.00 (R460,000.00). I concede that esketamine in isolation may have around five times the potency of its right-handed mirror image R-ketamine, but then the bioavailability nasally (at best 50%) cannot compare with that of the intravenous racemic mother compound. Bearing in mind that the aforementioned costs don't even include cost of monitoring in a clinical environment, this mode of administration is a non-starter in South Africa, particularly considering the exchange rate. There is no compelling evidence that the efficacy of intranasal esketamine exceeds or even matches that of intravenous racemic ketamine.

KETAMINE, SUICIDE, AND A VIRUS

The global disease burden of depression is massive. Ironically, authors of the most consequential of all antidepressant trials (STAR*D) back in 2006[5] predicted that in 2020, depression would be the second leading cause of disability globally. Subsequent researchers predicted that 2030 would see depression as the leading cause. Had these soothsayers only known about COVID-19, how might they have adjusted their predictions?

Reger *et al* in an article published in JAMA Psychiatry in April 2020[6] describe suicide mortality and COVID-19 as a *'perfect storm'*. Suicide hotlines around the world are reporting a threefold increase in calls. Given that South Africa already boasts a suicide rate four times the global average this uptick alone probably poses a risk to life greater than the mortality from the virus itself.

Consider that the unemployment rate in isolation corresponds to a linear increase in suicide rate – then add the isolation of lockdown, domestic abuse, and fear of the virus itself. It is hard to imagine depression and suicidality not reaching the top spot (certainly in South Africa).

"THE UPTICK IN THE SOUTH AFRICAN SUICIDE RATE SINCE LOCKDOWN WILL PROBABLY ACCOUNT FOR MORE MORTALITY THAN THE VIRUS ITSELF."

At such a time as this, if there were an affordable treatment that could offer a rapid and robust antidepressant effect with reversal of suicidal ideation in most cases, why would this remain in the wings? This is ketamine's time. Not at the expense of traditional monoaminergics, mood stabilisers and CBT but as an adjunct, and a crucial one at that.

"SUICIDE HOTLINES ARE REPORTING A THREEFOLD INCREASE IN CALLS SINCE LOCKDOWN."

STAR*D showed that only one third of patients respond to a single antidepressant, a further third requires up to four medications and the balance are termed 'treatment resistant'. Furthermore, the study concluded that for most patients, *'remission requires repeated trials of sufficiently sustained, vigorously dosed antidepressant medication'* and that physicians should *'give maximal but tolerable doses for at least 8-weeks before deciding that an intervention has failed'*. Is ketamine infusion not custom-made to offer remission during this period of tinkering? What of the one-third who remain 'treatment resistant'?

Is it not time, given the anticipated flood of newly diagnosed depression and exacerbation of the condition in existing sufferers to move racemic ketamine out of the shadows and into the spotlight in both the private and public sectors? This is already happening in the NHS.

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