Gendering Ketamine Use:
Emerging Research and Harm Reduction Recommendations
2024

The K-hole went straight on like a tunnel for some way, and then dipped suddenly down, so suddenly that Alice had not a moment to think about stopping.
(adapted from Lewis Carroll - Alice in Wonderland).

Paper endorsed by:

Introduction

This paper explores ketamine use with a gender lens to show how ketamine social and biological variance across genders begs a tailored harm reduction approach. Ketamine provides dissociative anaesthesia and analgesia, now also used in the treatment of depression. The dissociation is particularly specific to ketamine and explains its medical and recreational utility. While there are some robust generic sources of information on ketamine and harm reduction,[1] WHRIN and TalkingDrugs have identified a critical gap: the experiences of women and gender-diverse people are notably absent in much of the existing harm reduction guidance. While broad harm reduction advice and strategies exist around ketamine, the majority are provided with no consideration of gender-based differences. This oversight is concerning given identified differences in how ketamine affects individuals across gender spectrums and associated, distinct implications for harm reduction messaging.

Much of the existing research (of varied rigour and reliability) is pinned to predominantly male human subjects and/or rodent studies. While our quest is to identify gendered difference in recreational ketamine experience, much of the data comes from clinical administration rather than recreational use contexts. It is also important to note at the outset that within the scientific research on ketamine, where it acknowledges gendered differences at all, these are almost exclusively expressed through a binary understanding of sex.[2] Testing is done on female and male rats, for example, with little consideration as to how this binary may or may not apply to human beings and the diversity of genders and sex

characteristics contained within. Exploring ketamine use with a feminist and trans-inclusive lens means acknowledging the limitations of this perspective – because of the existence of intersex people; because of the variations in hormone levels within each assigned sex; and because drug use for all genders is shaped by patriarchy together with the gendered impact of drug policy and cannot be understood solely through biological mechanisms. While we rely on this research, we understand that it is hinged on understandings of sex and gender that are incomplete at best and that this will impact both the findings themselves and the types of questions that currently remain unasked.

Ketamine's unique synthesis in those assigned female at birth

Firstly, we focus on human-based research; in a study from Taiwan (one of very few focused on recreational use), women self-reported more discontinuation symptoms such as anxiety, dysphoria, and tremors (from ketamine withdrawal) than men. Women were also more likely to report cognitive impairment and urinary symptoms due to their ketamine use. However, of 1,614 people in the study, only 17% were women.[3] Further, the impact of ketamine on urinary symptoms was not replicated in a UK self-reporting study which showed no statistical difference between women and men.[4]

In the context of therapeutic ketamine administration, and although transient hypertension is expected with ketamine treatment, women experience increased diastolic blood pressure twofold faster and more severely than men. This finding indicates that people assigned female at birth with pre-existing hypertension should be aware of increased risk of hypertensive crisis in ketamine use.[5] Likewise, caution should apply when combining ketamine with other hypertensive substances such as stimulants.

Also, in human subject analyses, ketamine has been shown to have greater analgesic effects in men, whereas women have 20% faster clearance of the drug.[6]

Relying on rodent studies, it was also determined that 3 weeks of daily ketamine dosing can result in anxiety- and depressive-type behaviours among females, an effect not found in males.[7] Yet female rats that had undergone ovary removal developed similar anxiety and depression-like behaviours which were alleviated by ketamine doses, similarly to male rats.[8]

Hormonal influences

It is becoming evident that ketamine dependency and the likelihood of adverse events manifest in sex-influenced ways. Emerging rodent-based research shows oestrogen and progesterone significantly affect ketamine's impact, causing different reactions at various points in the menstrual cycle. (Oestrogen is a sex hormone responsible for the development and regulation of the female reproductive system. Progesterone is a hormone that supports menstruation and maintaining a pregnancy.) In sum, females are more sensitive to the effects of ketamine than males, and it might be possible to monitor the phase of the menstrual cycle to manage and control such variation. Ketamine use near the onset of the rat period, when oestrogen and progesterone levels are at their lowest, may reduce impact because ovarian hormones likely increase susceptibility to the effects.[9,10,11] However, an additional study found that inhibition of the startle reflex and spatial working memory as impacted by ketamine use were not observed in female rats in high-oestrogen states, suggesting hormonal cycles may dampen these particular effects of ketamine – yet affirming that there is a gender difference in the adult rat response to ketamine which is based on sex hormones and the menstrual cycle.[12]

Breast/chest feeding

One study was identified on ketamine in breast milk in the context of clinical dosing for postpartum depression among only four lactating participants. The findings showed low oral bioavailability with minimal exposure to infants and no adverse effects.[13,14] A larger study on infants of women who received ketamine anaesthesia for surgery likewise showed that ketamine use appears safe in lactating women and uninterrupted breastfeeding should be encouraged and supported.[15] However, infants should be monitored for sedation, poor feeding, and reduced wet diapers, and support sought should adverse effects develop. It is also important to note that there are no studies investigating the implications of using ketamine recreationally during breast/chest feeding.

Pregnancy

To date, there is a lack of controlled data regarding the use of ketamine during human pregnancy.[16] The available human data relating to depression therapy suggests that ketamine may be used in low doses to treat depression throughout pregnancy, although other treatment agents may be preferable.[17] Animal studies have demonstrated that ketamine exposure of pregnant rats is associated with affective disorders and cognitive impairments in offspring.[18] However, rats in this study were given intravenous ketamine slowly over 2 hours, which limits the applicability of the findings to human recreational use. Ketamine is also known to increase maternal blood pressure and heart rate by up to 30% to 40%.[19] As there are no human studies, general advice is to avoid non-medical ketamine use while pregnant.

Hormone replacement therapy (HRT)

The interaction between ketamine and HRT is not extensively researched. However, emerging evidence of the impact of sex hormones in ketamine experience opens avenues for further investigation, particularly regarding the implications for individuals undergoing HRT, including members of the transgender community, menopausal and post-menopausal people.

Gendered social risks

The dissociative, euphoric, and memory lapse effects of ketamine can put the user at risk of accidents and assault (both physical and sexual) and may increase the likelihood of having unprotected sex, increasing the risk of unplanned pregnancy and sexually transmitted infections. Ketamine is also noted among common date rape drugs.[20] Recreational ketamine use poses several distinct potential risks that disproportionately affect women and gender-diverse people, given the global climate of gender-based violence combined with the heightened and gendered risks faced by people who use drugs as a criminalised population. Risk factors include increased suggestibility, disorientation, impaired motor coordination, loss of consciousness, and diminished ability to provide consent, heightening the risk of unnoticed injuries and sexual exploitation and violence. Gender based violence prevention planning must build in consideration of issues facing women and gender diverse people who use drugs. Harm reduction staff can work with entertainment and night-time staff to promote safe and orderly night life environments[21,22] and can also support those at risk with information and planning tips such as preparing for safe sex, using in a safe environment, designating a non-using person to supervise and assist others, and watching your drinks.[23]

Ketamine and opioid pathways

Important sex differences have been identified in the way that ketamine interacts with opioid pathways in the brain in rats. Ultrasound imaging found that in males, blocking opioid receptors (through the drug naltrexone) also blocked ketamine's effects. In female rats, on the other hand, the use of naltrexone did not block the effects of ketamine.[24] This suggests that there are sex-specific relationships between ketamine, hormones, and opioid systems in the brain.

What explains this difference? It appears that female rats might have a compensatory response – that is, when opioid receptors are blocked, they are able to compensate by growing more opioid receptors. Male rats do not seem to have the same response. The presence of testosterone may play a role. When researchers removed the testes of male rats, therefore removing the source of testosterone, male rats responded similarly to female rats.[25,26]

These findings highlight the necessity of disaggregating data by sex in research on ketamine and considering the impact of hormone levels on ketamine's effects. More research is needed to better understand these pathways – otherwise results will be confusing, and gender-neutral treatment strategies could lead to unique risks in people assigned female at birth, gender diverse people, or anyone with changing hormone levels.

An important caveat is that ketamine primarily acts through NMDA receptors in the brain, so while these findings and others demonstrate a connection between ketamine, hormones, and opioid receptors, this activation is minimal compared to ketamine's activity at NMDA receptors. There are also interactions between these two systems.[27]

Because of the distinctive ways that ketamine may interact with opioid receptors in women, they may face heightened risks when combining opioids and ketamine. In general, multiple studies have found that opioids and ketamine have a synergistic effect, meaning that they increase the strength of one another.[28] However, the majority of these studies consider interactions between the drugs in a clinical context, not recreationally. They also do not take into account how hormonal differences and social and biological variance across genders may amplify or diminish the effects of ketamine. Further research is warranted to understand the implications for overdose, given the role ketamine plays in potentiating overdose in polysubstance administration scenarios.

Ketamine's antidepressant effects

Women suffer from major depression at twice the rate of men,[29,30] are more likely to seek treatment, and are more sensitive to antidepressants.[31] Ketamine therapy has been shown to positively benefit people experiencing treatment-resistant depression, including suicidal ideation, and is used with pre- and post-menopausal people as well as for alleviating post-partum depression.[32]

Female rats appear to be more sensitive to lower doses of ketamine (specifically at 2.5mg/kg), receiving more "anti-depressant-like effects" than male rats. These antidepressant effects disappear when female rats had their ovaries removed. Oestrogen and progesterone could be enhancing agents of ketamine's effect.[33,34,35] However, the mechanism through which oestrogen and progesterone potentiates the antidepressant effects of ketamine is unknown. There is a literature gap on sex-differences in ketamine clinical trials, needing deeper research.

A meta-analysis found that sex makes no difference at the 4hr and 24hr post-consumption time point with depression therapy doses; only at the seven day mark did human male subjects have a higher antidepressant effect from ketamine consumption (consumed intravenously). The review conceded, however, that there is a lack of understanding of post-7 day effects.[36] Gendered differences in response to ketamine therapy have been inconsistent and challenging to apply to humans, and this lack of understanding carries out throughout much of the ketamine research.[37]

Overall, it seems that the effects of ketamine (and its associated anxiety and depression-related benefits) dissipate faster in female groups than in male groups. And while with females, lower doses of ketamine are needed to create antidepressant effects, the repeated use of ketamine can increase susceptibility to dependency.[38] However, this is an inference from rat-based research and intravenously administered ketamine, which does not tend to be the preferred route of administration for non-medical use of the drug.

There are psychological well-being considerations for transgender and gender-diverse individuals using ketamine. Psychedelic experiences using drugs such as ketamine and transgender identities both have been medicalised and pathologised – even criminalised – by the Western medical model. Trans and gender-expansive people are vastly underrepresented in clinical research, and trials of psychedelic-assisted therapy are no different.[39] Ketamine therapy can increase gender affirmation[40] in multiple ways, alleviating negative consequences of gender dysphoria, fostering self-compassion, providing a pathway for reconnecting with oneself and others, as well as by addressing depression and anxiety.

Dosing

Dosage depends on the purpose of ketamine consumption. In small (sub-anaesthetic) doses, ketamine is used recreationally. In even smaller doses, ketamine relieves depression and can provide rapid resolution of suicidal ideation.[41]

Although it is difficult to ascertain accurate measurements in a recreational use context:

- Low doses (between 25-50mg) generate a serene state and are safest, as this low dose keeps you connected to your body and less likely to be at risk when in public settings.
- Medium doses (100-300mg) induce spatial disorientation and confused thinking, so having a safe environment for this dose is important.

- A high dose (300mg or more) can produce out of body experiences and hallucinations.[42] Again, a safe space, ideally with one person designated to support others, is recommended.

Ketamine has a high volume of distribution and so it is crucial to consider body weight when calculating dosage. Lighter people will experience the same effects with a smaller dose. Finally, while not yet possible to extrapolate directly to human experience, rodent-based studies demonstrate the heightened sensitivity that female rats have to ketamine's dosage and effects.[43]

Recommendations

There is much more to be learned about the effects of ketamine on women and gender-diverse people, and there is a corresponding need for the development of tailored harm reduction services. Much of the research on ketamine remains focused on men or rat testing, so more sex-disaggregated human investigation is needed to fully understand and manage effects. Further, most of the research considers ketamine in a clinical context, not recreationally, and without taking into account how hormonal differences and social and biological variance across genders may amplify or diminish impact.

Conduct gender-specific studies to further understand the pharmacological and psychological effects of ketamine. This includes assessing the impact of recreational ketamine use:

- in human pregnancy and lactation (in both clinical and recreational doses).
- according to the quantity of sex hormones in the bloodstream.
- for people undergoing hormone replacement therapy.
- with regard to opioid pathways, with sex as a key variable in consideration of tolerance and overdose implications.

Future research aside, harm reduction strategies that specifically address women and gender-diverse recreational users include:

- Harm reduction services can cooperate with night-time culture venue operators to build safer social contexts; collaborate with violence crisis counselling, accommodation and clinical centres to strengthen referral linkages for women and gender diverse people who use drugs; and provide tailored peer guidance for ketamine users at risk of gender based violence.
- Provide linkages to support programmes that safely implement the use of ketamine therapy for improving psychological well-being, such as the establishment of low threshold opportunities for access to ketamine for treatment-resistant depression and suicidal ideation.
- Extra attention should be paid to people assigned female at birth with baseline hypertension because of the increased risk of hypertensive crisis with ketamine use. Similarly, caution should apply when combining ketamine with other hypertensive substances such as stimulants.
- While there are no studies investigating the implications of using ketamine recreationally during breast/chest feeding, existing studies suggest that ketamine use appears safe in breast/chest feeding and uninterrupted feeding should be encouraged and supported. However, infants should be monitored and support sought should adverse effects develop.
- As there are no human studies, general advice has been to avoid non-medical ketamine use while pregnant.

References & notes

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